UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL ACTION NO 16-MD-2738(FLW)(LHG)

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| IN RE JOHNSON & JOHNSON POWDER PRODUCTS MARKETING, SALES PRACTICES. | : | DAUBERT HEARING<br>JULY 26, 2019<br>VOLUME 5 |

CLARKSON S. FISHER UNITED STATES COURTHOUSE
402 EAST STATE STREET, TRENTON, NJ 08608

B E F O R E: THE HONORABLE FREDA L. WOLFSON, USDJ

A P P E A R A N C E S:

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BY: P. LEIGH O'DELL, ESQUIRE (ALABAMA)
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On behalf of Defendant Johnson & Johnson

(Continued}

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A P P E A R A N C E S C O N T I N U E D:

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BY: THOMAS L. LOCKE, ESQUIRE (WASHINGTON D.C.)
On Behalf of Defendant Personal Care Products Council

M O R N I N G  S E S S I O N

THE DEPUTY CLERK: All rise.

THE COURT: Thank you. Good morning.

Would you call your witness.

MS. BROWN: Good morning, your Honor. We call Dr. Diette to the stand.

**GREGORY B. DIETTE**, called as a witness on behalf of the Defendants, having been first duly sworn, testified as follows:

DIRECT EXAMINATION

BY MS. BROWN:

Q. Good morning, Dr. Diette.

A. Good morning.

Q. We're excited to have you here today.

The Court already has your report and your CV as Exhibit C 18?

MS. BROWN: Your Honor, I can hand up another copy of the report and CV.

THE COURT: That would be great.

MS. BROWN: May I approach?

THE COURT: Thank you. You may proceed.

Q. Dr. Diette, I don't want to spend too much time

on your education and your experience, but would you at least introduce yourself to the Court and tell us who you are and what you do.

A. Sure.

Gregory Diette. I'm a full professor at Johns Hopkins University. I have appointments in the School of Medicine and the School of Public Health. I function in the traditional three roles there.

Q. You have three major roles at Johns Hopkins?

A. Yes. I see patients, outpatients in the clinic and also in inpatient settings as well.

I'm an educator. So I teach medical students, residents, fellows, the whole variety of trainees, and I'm a researcher. So I've had a full research portfolio for a couple decades.

Q. Are you, Dr. Diette, formally trained in the field of epidemiology?

A. I have a Master's degree from the School of Public Health.

Q. Do you do any teaching in the field of epidemiology nowadays at Johns Hopkins?

A. All sorts. I'm a mentor to various either junior faculty or fellows or residents. Part of that is teaching how to do a proper study, how to interpret it, how to report it.

I've taught in the classroom setting, for example a class called design of clinical studies that I co-directed. There are a variety of different lectures I give, and also just a lot of day-to-day hands-on support as well.

Q. You mentioned you are also a clinician, a practicing physician as well?

A. As well.

Q. Would you just tell us what that practice looks like?

A. It is a mixture of things.

I see outpatients that are referred to me in the clinic. I cover the physiology lab. The physiology lab is where we do exercise tests and lung function tests. I attend in the intensive care unit on the pulmonary service, taking care of pulmonary patients where we also do consults on every sort of patient in the hospital. I attend in the oncology center and then also the internal medical services as well.

Q. Have you conducted, Dr. Diette, your own epidemiology research?

A. Yes. It has been an ongoing process for the last couple of decades of doing a variety of human based research, which falls under the heading of

epidemiologic research.
Q. Can you give me the types of organizations or institutions that have funded your research over the years?
A. A mixture. The government organizations include NIH, the National Institutes of Health, Agency For Health Care Research and Quality, Environmental Protection Agency, and others, and then there's been private foundations and industry as well.
Q. Have you provided testimony to Congress concerning some of your epidemiology research?
A. Yes.
Q. Dr. Diette, has the focus of your own research been on ovarian cancer?
A. No.
Q. Does the fact that your own publications and research do not focus on ovarian cancer prevent you from being able to review and interpret the ovarian epidemiology at issue here?
A. Not at all. The approach to epidemiology is a fairly standard one where we are able to understand exposures of various sorts to understand all sorts of diseases and where there is risk or how to describe what the distribution of the disease is. It is important, too, in my teaching, in mentoring -- not

all of the teaching and mentoring is to people who take care of lung patients. I taught obstetricians, ear, nose and throat surgeons, ophthalmologists, the whole spectrum.

Q. Would you tell us, Dr. Diette, a little bit about your work with this MECOR organization?

A. That's an organization within the American Thoracic Society, and that society is our main lung society for professionals around the world. This is a program I participated in for many years where we teach epidemiologic methods to mostly physicians, but also doctoral students and some other medical professionals around the world how to do epidemiologic research.

Q. Have you participated in that program for a number of years now, Dr. Diette?

A. Several years. I traveled overseas many times to do that, and I've also done work in the United States when the mentees come to our conference each year to meet with them and help them with their research.

Q. The focus of that program is epidemiology?

A. Absolutely. We teach the basic methods. I was in charge of teaching advanced methods, and we also help them literally with their study design and with

interpretation of their findings and help them publish their results as well.

Q. Dr. Diette, do I always tease you about this picture where you are in front of a tree?

A. I don't know why. It is less pretentious than a white coat in a hospital. That's the one I have been using professionally.

Q. Okay. In addition to being a physician and an epidemiologist, do you also do some work consulting as an expert witness in litigation?

A. Yes.

Q. Can you give us an idea what percentage of your time you devote doing some of the things you are doing here today?

A. It varied over time. The first work I ever did was more than 10 years ago. Sometimes it is sporadic and sometimes there is more.

I would say currently between 10 and 20 percent of my time, which includes -- my time includes weekends and nights and holidays. So I'm talking about the full amount of time that's available to me.

Q. Do you do expert witness work only for defendants in litigation?

A. No, plaintiffs and defendants.

Q. Have you ever, in fact, Dr. Diette, turned down someone who has approached you to do expert witness work?
A. All the time. Pretty regularly.
Q. In terms of the expert witness work that you do, do you receive any assistance in terms of the administrative aspect of that part of what you do?
A. Absolutely. Everything in my professional life I depend on administrative support. My work at Hopkins I have administrative help, but I can't use their services for outside work. So I do work with a company called Medical Science Affiliates that provides administrative support to do various things to help organize the materials.
Q. Is it important to you to carve out some time to do some of the expert consulting work that you do?
A. It is for me. I like it quite a bit. It is very interesting work. It is a great window for me into the legal profession and a different way -- and sometimes having to converse with people and learning how to explain things.

I do notice it helps me back at Hopkins when I'm explaining things to patients. You are always trying to perfect your craft in terms of how to communicate. It all fits together. It is a nice part

of where I've got a very diverse career otherwise in terms of research, teaching, and patient care, this is one more aspect I find satisfying.

Q. Dr. Diette, just to kind of give us a framework for our discussion here this morning, what was your task here in this case?

A. We can see it on the slide here. It was to review the epidemiological literature regarding the hypothesized connections between talc or asbestos in talc and the development of ovarian cancer.

Q. Did you conduct an investigation into that hypothesis, and are you prepared to discuss with us your conclusions here today?

A. Yes.

Q. Are you prepared to do that to a reasonable degree of medical and scientific certainty?

A. I am.

Q. Just give us a brief understanding, what are your conclusions having reviewed the epidemiology on talc and ovarian cancer?

A. I think the overarching conclusion is that what it says here, the body of relevant epidemiological evidence does not support a causal connection between perineal use of talcum powder products, whatever constituents those products may contain, in addition

to talc, and ovarian cancer.

Q. Dr. Diette, were you able to come to court yesterday for a little bit of Dr. McTiernan's testimony?

A. I did.

Q. Did you hear quite a big discussion about relevant risk and confidence intervals?

A. Yes.

Q. Before we get to that, would you run through with us the methodology that you employed in terms of your own -- reaching your own opinions here?

A. Generally speaking, I used a variety of methods to try to find all of the relevant epidemiologic studies using search engines, reading the papers themselves, and looking at the citations in those papers, and trying to make sure I had all of the papers. I read and analyzed every single one of the studies.

I also looked to see where other professional organizations, how they had approached the issue where that was relevant, and then ultimately employed a Bradford Hill-type assessment of the evidence.

Q. And as part of your methodology, Dr. Diette, did you review internal Johnson & Johnson company documents?

A. I did not.
Q. Was that important for you in reaching a scientific opinion on the hypothesized connection between talc and ovarian cancer?
A. It is not a method I know that's part of an epidemiological investigation. So it wouldn't fit into that particular question.
Q. In terms of the discussion that we had here yesterday, Doctor, to orient us, you recall Dr. McTiernan speaking quite a bit about relative risks and confidence intervals. Is that right?
A. I do.
Q. And one of the things I'm hoping you can help us to understand is how findings in epidemiology studies are interpreted and reported and used in medicine. Are you prepared to do that, Dr. Diette?
A. Yes, I hope so.
Q. Did you come up with what you thought was a good example or a framework for that discussion?
A. Yes.
Q. Tell us what we are looking at and why you believe it is helpful to understanding how epidemiology findings are reported and used in medicine.
A. Sure.

There is a lot to know about this study, and I picked it on purpose. I thought it would illustrate to the Court the way that professionals in my field interpret and report findings routinely. So I picked a study that was one of the ones I had reviewed. It is relevant to this matter because it is about a potential risk factor in ovarian cancer. It's also relevant because it comes from the Nurses' Health Study, which is one of the sources of cohort data.

Q. Just to stop you right there, to orient us, this is a study that was looking into what? What was the investigation here?

A. The question was whether or not analgesics -- meaning aspirin and non-steroidal anti-inflammatory agents, things like Ibuprofen -- whether or not they are associated with the risk of ovarian cancer.

Q. What were the overall conclusions of the study?

A. Overall, it was kind of a mixture. Overall they found aspirin use altogether, there was no association; that it looked as if there was a protective association if you used low dose only, as opposed to conventional dose aspirin, and it looked like there was potentially a harmful effect from the use of NSAIDS for non-steroidal.

Q. This is a recent study. Right, Dr. Diette?

A. Yes. This is from 2018, which is part of the reason I picked it also because I think these authors are careful in their use of language as they interpret their findings. And so it tells us at least in 2018 in a good journal JAMA Oncology, the way that people are reporting findings.

Q. Does this paragraph that we have highlighted here contain a number of different epidemiological findings?

A. Yeah, it is great. It tell us really what their main findings are.

Q. Why don't you walk us through this paragraph and help us understand how epidemiologists like yourself take these numbers and translate them into a way to report and talk about their findings.

A. The first sentence that's highlighted, where it says "significant associations between aspirin and ovarian cancer risk were not observed." I would emphasize the "were not observed." It says, "When current versus nonuse of any aspirin was evaluated regardless of dose," and they have a hazard ratio, and the hazard ratio is analogous to a relative risk or an odds ratio. It is a little different measure, but it functions the same way. And so what they say the hazard ratio is .99 and so 1 would be no effect, and

here they have a 95 percent confidence interval that is .83 to 1.19. That includes 1.

So the language is important here. Even though it is to the left of that 1, in other words, pointing towards the protective side, they don't interpret it as protective. They interpret it as no effect, and that's in part because it's very close to 1, but also because the confidence interval includes 1.

If we go on, we will see, however, when low dose and standard dose aspirin were evaluated separately, an inverse association for low dose aspirin -- I'll pause there for a second. The inverse association is a hazard ratio of .77. That's below the 1 line. We can see the confidence interval does not include 1. That's where they use the language that "there is an inverse association."

Q. Doctor, if we could put some of these key take-aways on the flip chart, the sentence you are pointing to here is showing us a confidence interval that is less than 1. Correct?

A. That's right. The entire confidence interval is below 1.

Q. Tell us how epidemiologists like yourself report a finding like that where we are looking at a

confidence interval less than 1.
A. They use the word "inverse," and we might also use the word "protective" if that were appropriate which it would be in this case.
Q. If you are looking at a finding with a confidence interval below 1, in your field epidemiologists interpret that to be a protective or an inverse association?
A. Absolutely.
Q. Let's go on and see if we can understand more of the findings.
A. The rest of that sentence says: "But no association for standard dose aspirin." And here it is a hazard ratio of 1.17 with a confidence interval that includes 1.
Q. So here we have a confidence interval crossing 1. Is that right?
A. The confidence interval crosses 1.
Q. How do epidemiologists like yourself interpret a finding where the confidence interval is crossing 1?
A. This way. The way that they did, to say there is no association even though that hazard ratio is to the right of 1.
MR. TISI: Your Honor, this is not on the reliance list, and I believe they supplemented and we

objected to this.

MS. BROWN: Your Honor, for the record, in advance of Dr. Diette's deposition we did serve a supplemental list. This article is listed as No. 3. It was provided to the plaintiffs in advance of his deposition, and they had the opportunity to discuss --

MR. TISI: In advance of the deposition?

MS. BROWN: Yes.

MR. TISI: That's fine.

THE COURT: Thank you.

BY MS. BROWN:

Q. Picking back up where we were, and to orient ourselves, Dr. Diette, you were explaining to us in your world and in terms of real world understanding of these epidemiology findings a confidence interval below 1 is showing a protective or an inverse association?

A. That's right.

Q. A confidence interval crossing 1 -- and we spoke a lot about that yesterday with Dr. McTiernan -- would show or be interpreted as no association. Correct?

A. Exactly.

Q. Then if you continue on, do you have another finding to help us understand?

A. It is the final point here.

The last finding here is that current use of nonaspirin NSAIDS was positively associated with risk of ovarian cancer compared with nonuse. And here the hazard ratio is 1.19, but the 95 percent confidence interval does not cross 1. And so here it is a very, very similar hazard ratio to the one right before: 1.17 and 1.19 are nearly identical, but the words they use are important because they say there is no association for the 1.17 when it crossed 1. And they say it is positively associated in the one that did not cross 1.

Q. Dr. Diette, to round out our chart then this study and in your world, when we have a confidence interval greater than or equal to 1, that is reported as a positive association. Is that right?

A. It is. I thought this study showed it in a nutshell. It showed each one of those examples very succinctly and it came from a highly credible study in a highly credible journal, and it is current 2018. So this is the current way we express ourselves.

THE COURT: Thank you for that clarification, so I understand.

The fact that it is on 1 when you say cross, it has to have something before the 1, less than the 1 and across, that's the crossover. It can't just start

at the 1.

THE WITNESS: It has to go either from below up above it or from above down below it. Because the p-Values that --

THE COURT: I think I understand. It has to go on one side or the other to make it happen and that 1 is within it. It can't just have 1 as the number?

THE WITNESS: Exactly right.

BY MS. BROWN:

Q. To follow up on Her Honor's question, in reporting a positive association where the confidence intervals are equal to or greater than 1, the findings are interpreted as a positive association. Correct?

A. Correct.

Q. Just to refresh, where the confidence interval, as Her Honor was asking about, crosses 1, those findings are interpreted as showing no association. Right?

A. Exactly.

Q. And where the confidence interval, the entire interval is below 1, those findings are interpreted as showing a protective or an inverse association. Is that fair?

A. Exactly right.

Q. Now, another way to talk about these confidence

intervals, Dr. Diette, is to use the term "statistical significant." Is that fair?
A. It is.
Q. Would it also be fair, then, to say where your confidence interval is crossing 1, there is no statistical significance?
A. That's exactly right.
Q. Many of the studies that Dr. McTiernan put up yesterday had confidence intervals crossing 1; and would you interpret those to be non-statistically significant findings?
A. Yes. Each one of those for which that is true would be non-statistically significant.
Q. How would you then interpret that in sort of regular people's speak?
A. We would say there was no association found within that particular study.
Q. Does this mean, Dr. Diette, that we should draw a bright line at statistical significance and keep everything that reaches statistical significance and throw out any study that doesn't achieve statistical significance?
A. All the studies provide information, but it is one part of the information you get from the study.
Q. And in conducting your review of the

epidemiology as it relates to talc and ovarian cancer, did you employ a bright line rule to weight or value studies with statistical significance differently or better than those that did not reach statistical significance?

A. I tried to observe which ones were and which ones were not. I didn't exclude any in particular. I just noted which ones were and which ones were not significant.

Q. Why is it important for you as an epidemiologist to take note of whether or not a study is achieving findings that are reaching statistical significance?

A. Because within that particular study the authors of the study have conducted it in a way that they are going to be willing to communicate that the finding they have either does or doesn't endorse the idea there is a difference in the two groups they are looking at. And so this is the convention for saying there is not a difference that they can express.

Q. I know you had the opportunity to review some of plaintiffs' briefing in this matter. Is that right?

A. Yes.

Q. Did you see the argument that was being advanced in terms of abandoning the concept of statistical significance?

A. I did.
Q. Is that a concept you are familiar with in your field, Dr. Diette?
A. I have been familiar with that idea in my entire career.
Q. In your field is it generally accepted that we should abandon the concept of statistical significance?
A. No, not in July 2019. What you are discussing is something that is a proposition and that may happen. As of right now that is not the case.
Q. Have you understood this to be a theoretical discussion that has gone on in your world for decades?
A. It is a great one. The idea is that you are trying to have a system that explains something about your data, and this is the system we have right now. I think there is a good and appropriate craving for something better always, and I think that is what is going on.
Q. In terms of your work that you had funded by institutions like the National Institutes of Health, and other government associations, have you reported your findings in terms of whether or not they reached statistical significance?
A. Routinely, yes.

Q. In terms of your review of the talc and ovarian cancer epidemiology, were the findings in those studies reported with confidence intervals that would suggest or indicate whether or not those findings reached statistical significance?

A. 100 percent of the studies had either confidence intervals or p-Values or both which is conveying statistical significance.

Q. Dr. Diette, with this framework in mind, I want to ask you some questions about some of the conclusions in the epidemiology studies that you reviewed and relied on here.

Were you here yesterday, Dr. Diette, and did you hear Dr. McTiernan's conclusions about what the epidemiology shows in terms of causation?

A. Yes.

Q. Did you understand her opinion to be that based on the talc epi in part, that there is a causal association between talc and ovarian cancer?

A. That's what I understood.

Q. Do the epi studies themselves report on whether or not they have found a causal association?

A. I think there's a lot of cases where the authors appropriately point out to the uncertainty that still remains and it spans a couple of decades of reporting,

that sort of uncertainty.

Q. What are some of the examples of what the epi studies themselves conclude?

A. Those top two are two of the most recent meta-analyses. The first one says that it is unclear whether a statistical association exists; and, if so, whether it can be interpreted as reflecting some form of bias or causal relationship. So it is not clear it's been established by that statement there is causation.

The second one is a little clearer even saying --

THE COURT: You should use the names of the studies for the record. These are just PowerPoints right now.

Q. I'll jump in and help you on that score, Dr. Diette.

For example, if we look at the Berge 2018 article at A-11, page 3, what do the authors of that recent meta-analysis say about a potential causal relationship between talc and ovarian cancer?

A. Unclear whether a statistical association exists and whether it can be interpreted as reflecting some form of bias or a causal relationship.

Q. And one of the studies Dr. McTiernan referred to

quite a bit yesterday was a meta-analysis from 2018 by Penninkilampi.

MS. BROWN: And that is, for the record, located at A 109, page 3.

Q. What do the authors of that study say about whether there is a causal link between talc use and ovarian cancer?

A. That it has not yet been established.

Q. And in your review of all of the epidemiology studies, Doctor, do you see consistent conclusions to those which we just read?

A. I think they are appropriately concerned in the studies about whether or not causation can be established.

Q. I want to talk now about, Dr. Diette, in your report, which Her Honor has, and which we have marked as C 18, did you conduct a full Bradford Hill analysis?

A. I did.

Q. We've already had Dr. Neel in here addressing part of that and we have Dr. Saenz coming next week, so I want to concentrate with you on a couple of areas of that analysis today. Is that okay?

A. Absolutely.

Q. Let's start with strength of association. Why

don't you start by telling us, in your view, is that a good place to start when, when you are doing this kind of analysis?

A. It is a good starting point because the Bradford Hill considerations start with the notion that once an association has been established that that is the jumping off point for doing a Bradford Hill type of analysis. So the strength becomes one of the important anchor points of how you are going to proceed.

Q. Dr. McTiernan put up a slide yesterday that indicated that she weighs this Bradford Hill factor as one of the highest. Do you agree with that?

A. I do. I think this is a very high one.

Q. In your view, Dr. Diette, is it possible to properly apply the Bradford Hill criteria and conclude, based on this epidemiology, that the association between talc use and ovarian cancer is strong?

A. No. It is objectively weak in certain of the studies and not existent in others.

Q. First of all, is there a bright line rule in terms of what is a strong association and what is a weak association?

A. There isn't an exact cut-off.

Q. Do you get any guidance, for example, from the Bradford Hill article itself?
A. I think it was a very helpful way to express what he was trying to convey; where, for example, he mentioned a 200 fold increase was a large effect, and that also saying in cigarette smokers it was 9 to 10 times the rate of lung cancer in smokers compared to nonsmokers, and 20 to 30 in heavy smokers. Those I thought were good examples of what's clearly a strong association.
Q. You mentioned relative risks and odds ratio like 200 or 10. Is that right?
A. Exactly.
Q. Has there been a positive relative risk reported in all of the studies that have been done on talc and ovarian cancer?
A. Sure. In certain of the case-controls have a positive one.
Q. What number are we looking at in terms of the talc and ovarian cancer literature?
A. The summaries of that are in the 1.2 to 1.3 range.
Q. Have some of the authors of the talc epidemiology commented on whether that kind of a relative risk, 1.2, 1.3, is considered strong?

A. Yes. This is an example here from Berge saying their meta-analysis showed a weak but statistically significant association.

Q. One of the things we heard about yesterday, Dr. Diette, was instances like HRT and secondhand smoke where studies have produced a low relative risk. Were you here for that testimony?

A. Yes.

Q. Let's take those one at a time. In the case of HRT, are you familiar generally with clinical studies that showed about a 1.2 relative risk?

A. Yes.

Q. Help us understand how a relative risk that low could have supported a causal inference or causal association when it comes to HRT?

A. That story comes from first observational studies but was confirmed in randomized control trials. So when you find a small risk that you are looking for in a randomized control trial, that's a different circumstance for one. So that's really the best study design to confirm causation, and that's why there is confidence in that because of the study design.

Q. Why is a randomized control trial a better study design if you can do it?

A. Assuming it is properly done, it has the advantage of assigning people to the exposure as opposed to them finding their way to the exposure on their own. So it takes away the possibility somebody is different and, therefore, having exposure. This way you control for that. And it also helps to minimize, not eliminate, but minimize confounding, and it helps to minimize confounding of both known and unknown confounders, which is really important.

Q. We will talk a little bit about confounding in a moment.

But as a practicing pulmonologist, are you Dr. Diette, also familiar with the epidemiology regarding secondhand smoke?

A. Yes, generally, yes.

Q. Yesterday secondhand smoke was raised as an example of an area of epi with a low or weak relative risk that, nonetheless, has been found causal. Can you help us explain that?

A. Yes. The starting point for that was knowing already that tobacco smoke causes lung cancer. This was done in an era where the biologic plausibility or even certainty was well-established, and the authors of at least one of the studies that's been cited where they looked at passive smoke in homes said that was so

strong that's why they could interpret a 1.2 as being causal along with many other things where they found dose-response to be convincing, and many other Bradford Hill criteria.

So, as an example, where you still go through the Bradford Hill criteria, and you can arrive at a conclusion of causation, just like you can go through the criteria and not arrive at a causal conclusion.

Q. In terms of your review of the talc and ovarian cancer epidemiology, do you find it to be analogous to the epidemiology of secondhand smoke and lung cancer?

A. No, it is not.

Q. Dr. Diette, we were speaking a minute ago about some of the weak or low relative risks that were found in some of the case-control studies. Correct?

A. That's right.

Q. Can you help us understand how, in terms of a body of epidemiology literature, a case-control study fits?

A. It is a good study design. It is one of the two main observational study designs with case-control and cohort being the two. You can use them in different circumstances and you can talk about strengths and weaknesses, but Leon Gordis, who was one of my teachers, this is in addition to his book, he

describes case-control studies coming after somebody has made an observation or has the idea there might be some signal, and then says that the next step to elucidate the relationship is to do a cohort study to help confirm it, and gives a good example of where for a while people thought high fat diet increased the risk of breast cancer because there was a signal from case-control studies, and I think the odds ratio was about 1.6, but cohort studies were done and showed that wasn't the case, and now that issue has gone away because of that sequence. So this is one way they conceptualize. They have some similarities, but often they are done in sequence.

Q. In terms of the weak or low association seen in some of the talc and ovarian cancer literature, is that confined to the case-control studies?

A. It is.

Q. Tell us, were cohort --

THE COURT: I want to go back. I want to follow up on the question, the previous area where he answered the question.

You asked a question: In terms of your review of the talc and ovarian cancer epidemiology, do you find it to be analogous to the epidemiology of secondhand smoke and lung cancer? He said: No, it is

not. I want him to summarize why he does not.

Can you answer that question for me?

THE WITNESS: Absolutely.

Just to be clear, the starting point for both of those is a weak relative risk; and in both cases, investigators would be appropriately concerned that they may have found something that isn't causal, and they would be very worried especially because it is a weak risk about the potential for confounders and for bias and other issues.

In tobacco smoke, these studies were done so well into the general knowledge about tobacco smoke and lung cancer that that was no longer a question. Nobody --

THE COURT: I heard your answer to that. Now, we're going to move to your review of the talc study and why you don't find it analogous.

THE WITNESS: I have not seen anybody express that there is a body of evidence for talc as a carcinogen where that is already so well established where you would take any finding and say that is causal.

To go on, though, they also cited good consistent dose-response findings in the secondhand smoke study, and you will see later, but that is not

what I believe is shown in the ovarian cancer literature. I think consistency was found there, and it's not found here.

So it wasn't just one Bradford Hill criterion, and the way those authors summarize in their final paragraph is, they say there is an abundance of Bradford Hill criteria that are satisfied, and, therefore, that's why you should accept the small relative risk. I don't think there is that abundance for talc and ovarian cancer.

THE COURT: Okay. Thank you.

BY MS. BROWN:

Q. Just to sort of close the loop on what Her Honor was asking about, was there also a proven or understood biologically plausible mechanism by which cigarette smoke can cause lung cancer?

A. That was the point. That was well enough worked out in primary smokers that they were able to extrapolate that because it is basically the same smoke.

Q. In terms of how that relates to the talc epidemiology, in your review of the data, has there been a proven biological mechanism by which talc can cause ovarian cancer?

A. I have not been able to identify it. And I

noticed the authors of the epidemiologic papers also point to that as being not established.

Q. Doctor, we spoke a little bit about some of the case-controls weak or inconsistent, small, relative risk. What do the cohorts or the prospective studies conclude on that score?

A. For Gonzalez, they say, "douching, but not talc use, was associated with increased risk.

Houghton: "Based on our results, perineal powder use does not appear to influence ovarian cancer risk."

And Gertig: "Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall." And we know that was updated in the Gates study, which doesn't change that conclusion.

MS. BROWN: For the record, we will note the Gonzalez study is at A 47; the Houghton study is at A 65; and the Gertig study is at A 45.

Q. Dr. Diette, to round out our discussion of the strength of association, can you summarize your opinion based on your review of the totality of the evidence as to whether properly applying the Bradford Hill criteria would allow you to conclude that there is a strong association between talc use and ovarian

cancer?
A. I think you have to conclude that it is weak. One is the target. It is almost impossible to have a study land on 1.0. When you get close to 1, you are really getting remarkably low. It doesn't mean it can't be causal, but it makes you more concerned than if it is a larger one.
One of the things we didn't show on the slide for Bradford Hill is they gave an example for a low-risk, which he said was about twofold or a little less. 2-plus, I think most of my colleagues would call a medium or high risk. But in the ones, especially, in the low ones, that is objectively weak. That only comes from one study design, from the cohort studies, if you pool it, there is no elevated risk.
Q. Can you help us understand, first of all, when you are dealing with a low or weak relative risk like 1.2 or 1.3, are there challenges to determining causation in that context?
A. There are. This is a list of three of them. They are not only a challenge when you have a low estimated risk, but they are especially important when you have a low risk because they are very susceptible to distortion by these factors whereas a large estimated risk which has less chance of being

distorted, not no chance, but less chance.

Q. We'll talk a little bit about what that means. But in terms of identifying potential challenges to interpreting a low or weak relative risk, did IARC review this data and reach some similar conclusions?

A. They did. You will see at the bottom of that slide they said "chance, bias or confounding could not be ruled out with reasonable confidence." They raised the big three issues we grapple with in general.

Q. Give us an understanding, what does it mean that the chance or bias or confounding could be distorting a small relative risk like a 1.2 or a 1.3?

A. Chance is typically handled well by statistical testing, but there is always a chance every time you do a study, literally, you can get the wrong answer. You are literally taking a chance reaching the wrong conclusion. That happens.

Bias is a systematic factor that distorts the findings. It can drag the risk up or down depending upon which way it works.

Confounding are factors that are associated with the exposure that are the real cause rather than the thing you are studying.

Q. Is the concern about bias, confounding and chance heightened in a case where you don't have a

strong association?
A. Absolutely. A low association is very vulnerable to all three of those.
Q. I want to talk to you about bias and confounding.
Did you review the Penninkilampi study at A 109 as part of your work here?
A. I did.
Q. Does Penninkilampi comment on something called "recall bias"?
A. Yes.
Q. Tell us first what Penninkilampi says and help us understand what that means, if you could, Dr. Diette.
A. In this particular citation he says that "a limitation of the study is that it pools nonrandomized studies, primarily case-control studies, and that the retrospective nature of case-control studies introduces the potential for recall bias. In this case it's entirely possible that patients with ovarian cancer may be more aware of their previous talc use and hence may be more likely to report higher past use."
This is a 2018 opinion from an author after having performed a meta-analysis.

Q. And so explain to us -- I know we're going to look at an example in a minute. Explain to, in practice, what does "recall bias" mean, how does it work, and how does it happen?
A. There is a broader heading, which is an "information bias." Information bias is when the information that you get from your two groups -- in this case, the cases with the disease and the controls without disease. It's different information. And if it is systematically different that creates a bias. And that can come because of recall, not that you don't remember well, but you remember selectively. You have a different memory because you are sick and because you have an illness.
Q. Just to interrupt you there, Doctor, is it more likely when someone has been diagnosed with a disease and asked questions about habits or use of a product, are you more likely to remember you might have used it or something like that?
A. That's the notion. A classic example is a woman who gives birth to a child with a birth defect will rack their brain trying to think what might have happened during pregnancy, which is a very different experience than somebody who gave birth to a child without a birth defect where she may not have thought

about those issues at all.
Q. Dr. Diette, did you review the Schildkraut 2016 paper at A 129 as part of your work here?
A. Yes.
Q. Does the Schildkraut paper inform your opinion about the potential for recall bias in the talc ovarian cancer epidemiology?
A. It is amazing.
Q. Tell us what is amazing about this particular study.
A. A few things.

One is that we talk about recall bias more than we actually assess it. All my colleagues I know of are concerned about the potential for it in any case-control study. This is a rare example where these authors sought to demonstrate it, and they did demonstrate it, and they had a rationale where they believed because of lawsuits, that might have heightened awareness of talcum powder use, especially among women with ovarian cancer. So they chose 2014 as a date that happened in the midst of their study, and they thought 2014 would mark a line where women would suddenly become aware of the news about lawsuits.

Q. Did their study contain information where they

sought out to test whether or not that was true?
A. Yes.
Q. Tell us, if you could, did you put together a graph to help us understand what they did?
A. I did.
Q. I can give you the pointer if helpful.
A. I don't need it.
Q. Can you help us understand what they did in the Schildkraut article and how, if at all, that speaks to this idea of recall bias?
A. This comes directly from the study itself. On the vertical axis is the percentage of women who reported using genital talcum powder, and then cases are in the yellow/gold color, and controls are in the blue.

The left two bars are before 2014 and the right two bars are after 2014.

There are a few things to observe here. One is before 2014, it was actually a very similar proportion of women who reported talcum powder use, and what's up above is a calculated relative risk which is 1.19 and not significant before that date.
Q. Just to go back to our cheat sheet here, we have a relative risk of 1.19 and we have a confidence interval crossing 1. Right?

A. Yes.
Q. To find it on your chart here, how would that finding be interpreted?
A. You interpret that finding as no association.
Q. All right. Go ahead.
A. And then after 2014, there was an abrupt change in the reporting of cases. So it went from a little over a third to a little over half of women now saying that they had used talcum powder, if they happened to have ovarian cancer. And you will see the rate of that in the controls was basically identical to what it had been. It is a really dramatic effect all of a sudden pre-and post-2014. And these authors are the ones who chose that based on what they thought about.

The relative risk in that period is almost 3. It's 2.91, and it is statistical significant. Their positive finding is confined to post 2014, and they have a test I've highlighted down below. It is a statistical test that tells whether or not there is an effect of that change in the years, and by the statistical test they have done they say it is statistically significant with a P of .005.
Q. Before I ask you what that tell us, Dr. Diette, if I understand you, the number of people who did not have ovarian cancer who reported talc use before 2014

and after 2014, how would you compare those?
A. The talc use --
Q. Before and after, was it different? Was it the same?
A. For the controls it was essentially the same. For the cases it was dramatically different all of a sudden.
Q. What does that tell you as it relates to this concept of recall bias that we have been discussing?
A. It's extraordinarily consistent with it. This now goes into my teaching files. The authors have done a careful job of explaining why they looked for it, and they found exactly what they were looking for, and it is a differential effect in cases. So people who have the disease who change their reporting abruptly, it's highly consistent with that.
Q. Before we close out recall bias, in terms of when you are looking at a relative risk of 1.2, 1.3, what does something like that suggest could be doing to that number? How does that work out in real life?
A. This is recall and recall related to lawsuits. It also could illustrate the same effect that could be happening for recall for other reasons or reporting differences.
Women and people in general report about

sensitive topics differently. It illustrates the idea there could be a reporting difference in people based on something about them.

Q. What does it suggest in terms of a positive association? Does that suggest to you that that association is true or real or something else?

A. It is only true after 2014 in this study, and it is really -- we have seen there's various entities and authors who have worried about the potential for recall bias. This proves it's real in at least one of the studies.

Q. One of the other things that was indicated in the IARC assessment of this epidemiology was something called "confounding." Is that right?

A. That's right.

Q. Can you explain to us what that is and why we have a beer bottle and a cigarette?

A. Yes. Confounding refers to a factor which is associated with the exposure itself that also is a cause of the outcome you are looking at, and it matters whether you can account for it or not.

So the example I have here is made up. If you were to do a study of a beer drinker and lung cancer, you may well find there is a positive risk. We don't believe beer causes lung cancer, and we know some

people go to bars and drink and smoke at the same time. So you want to account for the smoking. The smoking would be the confounder. That's the real cause of the lung cancer.

Q. How has this idea of confounding been addressed or captured in the talc ovarian cancer epidemiology?

A. Confounding has been handled in almost every single study to a certain degree. There's about five or six that I think one of the meta-analyses identified as being uniformly or almost uniformly accounted for, but there are many that are potentially important that aren't accounted for in most of the studies.

MR. TISI: Objection, your Honor. His expert report does not talk about any other factor other than douching. It does not talk about family history, socioeconomic status, hormone therapy, family history of breast cancer. It only talks about douching as a confounding factor, and that's what we're prepared to discuss with him today.

MS. BROWN: Two things on that, your Honor. Certainly he is speaking about the confounding factors that were addressed in the talc ovarian epidemiology which had been fully disclosed and counsel had the opportunity to question Dr. Diette about. There was

also a discussion about potential confounding factors at his deposition. This is entirely consistent and based on the very literature that was disclosed.

THE COURT: At his deposition where there was a discussion about confounding factors, were these other items mentioned?

MS. BROWN: I believe so, your Honor. We will check right now.

MR. TISI: If they were mentioned, they were mentioned in passing.

MS. BROWN: To help the Court and move this along, I will right now confine the discussion to douching.

MR. TISI: Douching was discussed in his report.

THE COURT: She's agreed, and everyone can look back at the deposition and confirm as well if it was discussed.

BY MS. BROWN:

Q. Dr. Diette, confining yourself then just right now to the potential confounding factor of douching, can you help us understand how that plays out in the talc/ovarian cancer epidemiology?

A. Definitely. We know about the Gonzalez study.

Q. What were the findings of that and how does it

relate to this issue?
A. The Gonzalez study examined douching and talc use as a potential risk factor, and they found that douching was positively associated with ovarian cancer, and they found talc was not. They found that the two habits were associated with each other. So that women who douched also tended to use talc, and vice versa. So there was a strong relationship between the two.

Although that study found a risk for talc, that was less than 1 in that study, they still concluded the douching might turn out to be important. They gave reasons for it in terms of some potential plausible reasons, and they also said if the earlier studies had not accounted for that they may have missed an important confounding factor.
Q. Based on your review of the talc and ovarian cancer epidemiology, were there a set of consistent potential confounders that were addressed in those studies?
A. It wasn't consistent. It varied from study to study. Even the accounting for confounders wasn't uniform. So even if someone was going after the same basic concept, they didn't necessarily use the same indicator or the same measure of that particular

confounder.

Q. What's the significance of a potentially inconsistent controlling for confounders in a body of epidemiology like this with a low to weak to inconsistent relative risk?

A. It matters a lot, and it matters for a couple of reasons. One is because confounding factors have a much greater potential to distort the findings with a low risk, and that is especially true in something where the majority of cases of ovarian cancer don't have a known risk.

So most occur without a known high risk. So most of the potential confounding is not known. And, so, there are really two reasons why this becomes very important in this particular matter.

Q. Dr. Diette, before we move on to a discussion of dose-response, I wanted to ask you one more question on recall bias. We were addressing that in the context of the Schildkraut study, do you remember that?

A. Yes.

Q. There the inquiry was whether an individual was reporting talc use pre-and-post lawsuit media attention in 2014. Do you recall that?

A. I do.

Q. Is recall bias something that could exist in the epidemiology separate and apart from the 2014 media attention on talc and ovarian cancer?
A. Yes, of course.
Q. Can you explain that to us, please?
A. I would broaden that to say information bias. We're talking about case-control studies, for example, where the signal is found, right? And in every study where I could find whether it was acknowledged or not, there were interviewers who administered the surveys.

Another form of bias introduced by interviewers who know the status of somebody's disease at the time they interviewed them. So it's another way to change what the information is that comes out by probing more thoroughly when you know somebody has cancer. So the information bias as a general term could be quite different and recall bias can occur on its own without any media reports.

Q. Were most of the case-control studies conducted through that interview process you just discussed with us?
A. A majority were. I don't know I can find for sure they mentioned that as a method in every one, but for the most part it was interview administered.
Q. We heard some discussion yesterday from

Dr. McTiernan about the survey process by which members of the cohort studies were asked about their habits. Were you here for that, Dr. Diette?

A. Yes.

Q. Tell us about how the survey process could or could not affect the reliability in the cohort studies.

A. One thing I would say, self-administered surveys are not a feature of cohort studies. They were in these cohort studies, but they are not a feature. Either of these studies designs could use self-administered or interview administered or both in the study.

Because we are talking about a sensitive topic for some people, some women may be less forthcoming about personal hygiene habits and I would say that is especially acknowledged that issue in controls in general, I'm not talking about just in this matter, who have less at stake in that study, may be less forthcoming about what their personal habits are. So with an interviewer there face-to-face, there is a little bit of loss of privacy, so that can also induce a little bit of a change as well.

Q. I want to talk a little bit about dose-response. Was this part of your review of the talc epidemiology?

Did you consider the Bradford Hill criteria of dose-response?

A. I did.

Q. Give us an understanding what your opinion is as to whether the talc epidemiology shows a dose-response.

A. There is a lot of information to consider. One is that none of the cohort studies -- none of the prospective cohort studies showed a dose-response. Where there were case-control studies that had some estimate of dose-response, the results were highly variable. So there were a few that purported to show a positive dose-response. There were also some that showed a negative dose-response, meaning the more you used, the lower your risk.

There is an example in my report of basically a horizontal dose-response meaning there is no change up or down no matter what your dose was.

Then we have some examples of some really bizarre relationships. So these are just three specific studies. I'll say it is Cook, Mills and Rosenblatt.

MS. BROWN: For the record, Cook is at A 21; Mills is at A 94; and Rosenblatt is at A 125.

Q. Help us to understand, if you could, what we are

looking at in terms of these three exemplar studies found when it comes to dose-response.

A. To be clear, each of these is using a different scale. But from left to right on each one, you go from lower amount to higher amount of exposure. What you might expect to see is that in the lower left of each one of those figures it would be the lowest point; and the upper right would be the highest point, if there is a positive dose-response. If it is negative, it might go from upper left all the way down to the lower right.

But here there are things that don't make any sense to me biologically, like why the third category would have the lowest risk on the Cook one, and why the first and fourth categories would have the same risk. These are just examples. But in the context of there being both positive, negative, no, and haphazard, it is really a mess. It is all over the place, and it is not very reassuring that a dose-response relationship has been established.

Q. Is a dose-response relationship required for a causal association?

A. Not required, but it is one important criterion.

Q. How did these findings as you described them to us on inconsistent or variable dose-responses in the

talc epidemiology inform your opinion in this case?
A. I saw them as highly inconsistent, and it made me very worried about whether or not the investigators had measured properly what they had hoped to, or that there is in fact no causal relationship, and this is just what happens when you don't have a causal relationship.
Q. Did some of the studies themselves comment on whether or not the authors, having conducted their own study, found or did not find a dose-response?
A. Yes.
Q. Would you highlight some of those for the Court, and we will also read the exhibit number.
A. For a shorter one, the Health Canada from 2018, there is a lack of an available exposure effect relationship in the human epidemiologic data.
Q. For the record, Health Canada is A 58.
A. Houghton, this corroborates our results, there was no statistically significant risk with increasing duration of perineal powder use.
Q. At A 65.
How do these findings inform your opinion, Dr. Diette?
A. I think the authors of various studies are pointing this out because it is important, and one

would expect to see a dose-response. As you said, it is not required, but you would expect to see one for an exposure that's causing a disease.

Q. The final category as it relates to the Bradford Hill analysis that I want to discuss with you is consistency.

Can you tell us, No. 1, did you find consistency in your review of the body of literature related to talc and ovarian cancer?

A. I didn't. That's an important question because you said the body of the evidence. So this is not an exercise of just trying to find consistency here and there, or a couple of examples of a couple of things that happened to agree, but really looking at the total information you have available.

Q. And so explain to us: Did you attempt to evaluate whether there was consistency in a number of different areas that touch this area of scientific inquiry?

A. Yes.

Q. Let's start with study design. Tell us what your inquiry was there and what it showed?

A. Basically, the weak signal comes from case-control studies only, and that there is not a signal from cohort. So when you do the retrospective

studies you have a weak signal; and when you do the prospective studies, you have no signal, and that's inconsistent by study design. The different study designs produce a different result.

Q. You next have listed "condom and diaphragms." Tell us what you are referring to here and how that informs your analysis.

A. Since the general notion here is about perineal application of talc and whether it migrates to the ovaries and then causes some harm, many but not all investigators looked at some other ways to get talc up towards the ovaries, so in this case things that would go directly into the vagina. And so condoms and diaphragms we're looking at, and for the most part were either less than 1, but there was not a consistent signal that there was harm or a positive risk from these. So that was inconsistent with the notion that talc in the genital tract would lead to ovarian cancer.

Q. And dose-response we just discussed. Right, Dr. Diette?

A. Yes.

Q. Did you find those findings to be consistent or inconsistent?

A. Inconsistent, as we just showed.

Q. On your list you have tubal ligation. Tell us what that is and how that informs your assessment of consistency here.

A. Many investigators considered if you interrupted the female reproductive tract, you would block the pathway from the perineum to the ovaries. So by tubal ligation, you are cutting off the route through the Fallopian tubes. If the idea was correct, that perineal talc migrates, this ought to interrupt that exposure to the ovaries, and there were inconsistent findings. There were some positive, some negative, but not consistent.

Q. What you are saying, Doctor, is if the proposed biological mechanism or exposure pathway by which talc gets to the ovaries is migration, if a woman has a tubal ligation, that would prevent a particle from traveling through the Fallopian tubes to the ovaries, if this theory were true, you would expect to see a decreased risk in women who had tubal ligation. Is that right?

A. Yes, inconsistently. So some studies showed it and some did not.

Q. Finally, Dr. Diette, you have NSAIDS on the list. Tell us how that informed your determination about whether or not the consistency factor of

Bradford Hill was met here?

A. There were several studies that considered -- or were conceptualized as anti-inflammatory drugs, and there were a mixture of findings. So some positive, some negative, including the study that we looked at first, which actually had a positive risk for NSAIDS use, meaning that there was higher risk of ovarian cancer, which is inconsistent with the idea that NSAIDS would be protective against ovarian cancer.

Q. I want to show you something Dr. McTiernan used yesterday, which is this forest plot. Have you seen something similar to this in some of the scientific papers?

A. Yes.

Q. One of the things you'll recall from Dr. McTiernan's testimony is that she suggested that the findings of these epidemiology studies show consistency. Were you here for that?

A. Yes.

Q. In your view is that correct, Dr. Diette?

A. It is not. I think especially if we look down at the cohort studies, there is something that for me at least is a little misleading there which is to show Gertig, Gates and Gates all in a row because it's basically one study. So it makes it look as if

there's five studies.

If we look at the most recent one, which is the 2010, that box is a little to the right of 1; the Houghton study is a little to the right of 1; and Gonzalez is to the left. I don't find that to be consistent within the cohort studies.

Q. What about the suggestion, Well, a whole bunch of these studies have some point estimate around 1.2; therefore, this entire body of epi is consistent. How do you interpret this body of literature?

A. A couple of things. It is not fully consistent even if you summarize the risk for the case-control studies. But it is also compatible with what many investigators are worried about, which is risk of bias and confounding, which is you would expect to see it driving the same direction. So this wouldn't be a surprise if you had, for example, recall bias or confounding driving it a little bit to the right.

Q. If we could go back to the PowerPoint a couple of more areas I want to finish up with you, Dr. Diette.

As it relates to study design, did some of the meta-analyses like Berge 2018 comment on whether what they were finding in case-controls versus cohorts were consistent or not?

A. Yes.
Q. Is Berge A-11 -- tell us what those authors concluded on that score?
A. This points to one of the points we were making on the prior slide. Several aspects of our results, including the heterogeneity of results between case control and cohort studies, however, do not support a causal interpretation of the association.
Q. Did you consider what the authors themselves found on the consistency score when it came to doing your Bradford Hill analysis? For example, what the Berge authors concluded here.
A. Oh, yes. This is the same concept I'm talking about.
Q. On this point, Dr. Diette, as we talked about with strength of association, in your opinion, could you properly apply a Bradford Hill analysis to this epidemiology and conclude that the findings are consistent?
A. No.
Q. Give us just a brief explanation of why that is.
A. Because I think consistency is a global issue, and just finding consistency between a couple of studies is not enough. These are broad categories of inconsistency. So when the study design helps to

determine what the result is, that's a big inconsistency. When dose-response is all over the map, that's an inconsistency. These are examples of things where I don't think you can pool all of the information that's available and say that is a consistent finding.

Q. Two quick areas before we conclude here this morning.

You mentioned earlier a part of your methodology included looking at organizations and public health authorities like IARC that have reviewed the talc epidemiology. Is that right?

A. That's right.

Q. There was a suggestion yesterday that talc may contain asbestos. Did you hear that from Dr. McTiernan?

A. I did.

Q. Did IARC conduct some epidemiology studies that you reviewed as part of your work in this case that informed your opinion on that score?

A. They didn't conduct it, but they highlighted studies they thought would be most informative for that issue.

Q. Explain to us what those studies were and how they informed your opinion.

A. They pointed toward studies of miners and millers of the source of talc with the idea being these would be workers who would have really quite high exposures, and they said because of that, that would be a good place to look for cancer, if it was in fact a carcinogen.

Q. Did those studies of the talc miners and millers, did they investigate whether those folks were getting traditionally asbestos-related diseases like mesothelioma?

A. They did.

Q. What were the findings?

A. No mesothelioma in these studies from Vermont and Italy and Austria and France.

Q. Was this data included in IARC's review of the cosmetic talc epidemiology?

A. It was.

Q. And did this inform in part IARC's determination as it relates to the talc epidemiology recall chance and bias could not be ruled out?

A. It was one of their conclusions, but this informed their opinion that talc at least from these sources was not a carcinogen.

Q. Dr. Diette, did IARC also look at data regarding something called talc pleurodesis that Dr. McTiernan

discussed yesterday?
A. Yes.
Q. As a pulmonologist, have you instructed others to perform talc pleurodesis or performed it yourself?
A. I have done both.
Q. Give us a little understanding of what the procedure is.
A. Sure. This picture represents a couple but not only the forms that we get it in. What we get is talcum powder in order to put it into the space between the chest wall and the lung. We do it by making a small incision in the chest wall and basically squirt it in there and leave it in there long enough for it to have the therapeutic effect we are looking for.
Q. As it relates to whether or not this procedure has caused cancer in individuals who have undergone it, have you reviewed IARC's review of the literature on that?
A. I've looked at IARC, and also since then I've looked for anything newer.
Q. Tell us what the findings are as it relates to whether or not injecting talc into the pleural space causes cancer.
A. It does not appear to cause cancer.

Q. Have folks who have undergone talc pleurodesis been followed for decades to investigate that point?
A. There are a few studies that have looked for decades, and there is a whole variety of case series and case reports as well.
Q. Dr. Diette, could you then finally summarize for us your opinion and review of the totality of the evidence as it relates to what we asked you to do here, investigate the hypothesized connection between talc and ovarian cancer?
A. The only signal I see is the pooled relative risk from certain of the case-control studies and otherwise -- which provides a weak association. From the cohort studies we get no association. And I think the other Bradford Hill criteria have serious issues with them that don't support there being a causal link between perineal talcum powder and ovarian cancer.
Q. In your view, could a scientist properly apply the Bradford Hill criteria to the talc epidemiology and conclude that there is a causal association between talc and ovarian cancer?
A. It doesn't make sense to me.
MS. BROWN: Thank you very much for your time, Dr. Diette.
Unless your Honor has an area of inquiry, I'm

all done.

THE COURT: I think they have something for you.

MS. BROWN: On the objection that counsel made to the socioeconomic status, it is actually disclosed as an opinion in his report at page 21.

THE COURT: I saw it. I think that was the only one, and I did see it is in his report. That was on the confounding factors.

MS. BROWN: Thank you.

THE COURT: I did not see anything else on it. You did not want to follow up on that to confirm that.

MS. BROWN: I'll do it real quick.

BY MS. BROWN:

Q. Dr. Diette, just to revisit this idea of potential unknown or uncontrolled for confounders, we had on the slide socioeconomic status. Can you help us understand what that means and how it relates to the talc epi?

A. Sure. There is a paper by Alberg that I cited which points to low socioeconomic status being a risk factor for ovarian cancer. That's typical of many kinds of illnesses in the United States, that lower socioeconomic status confers a risk for all sorts of diseases. What's hard about that is that low

socioeconomic status is a complex phenomenon; it could mean low income; it could mean low education; it could mean different food, different jobs, different places where you live -- all sorts of different things that all sort of coalesce together to make somebody have a higher risk.

In most of the studies I saw there was not measurement of socioeconomic status, and where there was there was a crude indicator. It might have been education, which is a proxy for it, but it really doesn't fully capture everything about socioeconomic status. So that's one more important potential confounder that is undercovered in these studies.

Q. The final question, Dr. Diette, is how does that relate -- and when we are dealing with a disease like ovarian cancer, how important is something like a confounder like socioeconomic status that may not have been controlled for in some of the studies?

A. It is one more thing that would be missing from the question, especially with a low or weak risk that will distort the findings.

MS. BROWN: Thank you, your Honor.

THE COURT: We'll take a break now before we start the cross. It was an hour and a half. So you've got three hours.

We're going to take a break. So you can step down.

THE DEPUTY CLERK: All rise.

(Recess.)

(Continued on the next page.)

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THE DEPUTY CLERK: All rise.

THE COURT: Thank you.

**GREGORY B. DIETTE,** resumed.

CROSS-EXAMINATION

BY MR. TISI:

Q. Good morning, Dr. Diette.

We met at your deposition. Good to see you again. I kind of had a plan I was going to go at, but I'm going to tackle first things first.

A. Okay.

Q. The first epidemiology study that addressed the issue of ovarian cancer and talcum powder products was 1982. Correct?

A. That's my understanding.

Q. There has been about 40 years of research since then?

A. Just about.

Q. One of the last questions Ms. Brown asked you was whether or not no reasonable scientist could reach the conclusion that talcum powder products cause ovarian cancer in 2019. Is that your testimony?

A. It is.

Q. Could you please do me a favor and take out the Penninkilampi study, please. That is Exhibit No. 62

in your binder.

The Penninkilampi study, if you go to the conclusion, Ms. Brown asked you to read a sentence out of it.

Let me ask you whether the Penninkilampi study says the following. This is just to orient us. This is a meta-analysis. Correct?

A. It is.

Q. It says:

"The results of this review indicate that perineal talc use is associated with a 24 to 39 percent increased risk of ovarian cancer."

Did I read that correctly?

A. You did.

Q. (Reading.)

"While the case-control studies are prone to recall bias, especially with intense media attention following commencement of litigation in 2014, the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association."

Do you see that?

A. I do.

Q. Is that an incorrect statement?

A. There is more than one there. Are we talking

about the last statement or everything there? It is not disputable that the association that they estimate from this ranges --

Q. Doctor, is it suggestive of causal association?

A. I'm just clarifying. You read a lot of stuff. I just want to know what I'm reacting to.

Specifically, we are saying --

Q. Is it suggestive of a causal association? Is that what the authors say?

MS. BROWN: Your Honor, could he be permitted to finish his answer?

THE COURT: Mr. Tisi, we're just starting. Let him answer. And he is right, there are several sentences you read with different ideas in them. So let him break them down and answer it.

BY MR. TISI:

Q. I will rephrase the question, if you don't mind.

Do the authors conclude that the data they reviewed in this study is suggestive of a causal association?

A. That particular finding they say is suggestive of a causal association.

Q. If you go to the front page of this in the conclusions it says:

"In general, there is a consistent association

between perineal talc use and ovarian cancer."

Do they say that?

A. They do.

Q. You disagree with that?

A. Well, I don't know. Within the boundaries of this paper, for example?

Q. This paper reviewed all the studies, did it not?

A. No, it didn't. They left out an important one. But they reviewed many of the studies.

Q. Do they also conclude that because there was a specific association with a particular type of ovarian cancer that that mitigated against recall bias?

A. They did say that. I wasn't done with the one before.

THE COURT: There was no answer to that yet. He wanted to clarify he meant within the term of this paper. There wasn't an answer.

A. They don't tell what specifically they are using for it in general. But they did have an estimate that includes pooling all of the studies together, meaning the case-controls and the cohort studies. Those when you pool them together, might support that statement. If you look at the case-control separately, as they often did from the cohorts, you get two different answers to that. So I'm assuming they're talking

about if they pooled two heterogeneous groups of studies, they get an overall finding that way.

Q. Did the authors address the issue of heterogeneity?

A. They did.

Q. Did they find there was heterogeneity?

A. I didn't see a test of heterogeneity for the study design I don't think. They comment on whether there is heterogeneity by outcomes.

Q. Doctor, you've written a 51-page report. Correct?

A. That sounds about right.

Q. This report is dated February 25th of this year?

A. I'm sure it is.

Yes, it is.

Q. The methodology used to analyze the causal question in this case is the Bradford Hill criteria?

A. That's part of the methodology.

Q. You agree the Bradford Hill criteria is a framework that epidemiologists use?

A. I do.

Q. And you agree, is there any important epidemiologic study that you considered in your analysis that you believe the plaintiffs' experts did not?

A. I don't know. I didn't try to make an accounting of which ones which expert considered and which ones they didn't. So there are many plaintiffs' experts here. Right? Are we talking about folks who focused on epidemiologic studies?
Q. Yes.
A. I don't recall if there was one that was left out. I would say that I think each of them acknowledge the meta-analyses, including the more recent ones, which I think look like they have a pretty complete list. So either directly or indirectly I think they've accounted for the epidemiologic studies.
Q. The Bradford Hill analysis also involved consideration of biologic evidence as well?
A. It does.
Q. Can you think of any important biologic study you considered that any of plaintiffs' experts did not since you criticized them in your report?
A. Could you be specific?
Q. Did you identify any? I just want to know if the world of studies you looked at is exactly the same for the most part in terms of the major studies that the plaintiffs' experts looked at.
A. I didn't memorize the list of studies they

looked at.

Q. So you haven't identified any you think was a major omission that they did not consider that you did?

A. For a biologically relevant study?

Q. Right.

A. I don't recall any that I saw that they left out.

Q. Now, there were studies you left out. Correct?

A. It depends upon what do you mean by "left out"?

Q. We received two days ago a supplemental reliance list --

MR. TISI: Can you bring up PSC Diette 2. We were provided --

MS. BROWN: Your Honor, if I may, counsel objected to this list, and pursuant to that objection we didn't use any of these studies on direct. So I would object, if I could, to the use of a list that per agreement none of those studies were referenced on direct.

MR. TISI: I am not going to use them except to say they were not part of his initial analysis.

THE COURT: Are any of the ones on their list, studies that were available at the time he wrote his report? You can ask that. Ask that question.

BY MR. TISI:

Q. Are there studies on this list that were available at the time you issued your report?

For example, Henderson 1971. Was that available?

A. Yes.

Q. The title of that is "Talc and Carcinoma of the Ovaries and Cervix." Do you see that?

A. Yes, I do.

THE COURT: We don't have to go through all these. You can just look at the list. We've already gotten some answers, and I think the question is whether they were cited or not.

Did you read them or consider them when you wrote your report, those that were available before you wrote your report?

THE WITNESS: For sure some of these. I can't be sure all of them I read before the report.

BY MR. TISI:

Q. No. 2, No. 4, No. 5, No. 6, and No. 7 all deal with inflammation and talc. Correct?

A. They probably all have some bearing on inflammation.

Q. You have a section in your report dealing with inflammation as a potential biologic mechanism for

inducing ovarian cancer. Correct?
A. There is a topic about that.
Q. Several pages, single-spaced pages, talking about the evidence. Correct?
A. Can you point me to it? I want to make sure we're looking at the same thing.
Q. If you go to page 40.
A. I'm with you.
Q. You go on for several pages on inflammation and the biologic plausibility of talc inducing inflammation?
A. If several is 2 1/2, I agree with you.
Q. None of these studies are discussed. Correct?
A. Not here.
Q. Now, you understand the purpose of this particular hearing is to focus on methodology and not conclusions. Correct?
A. That's what I've heard.
Q. We're not here to determine whether or not your conclusion is correct, or, for example, Dr. McTiernan's conclusion is correct. Correct?
Do you understand that?
A. I'm not sure that's entirely true one way or the other, but I believe you.
Q. Let me ask you this, Doctor: Would you agree

all studies, irrespective of design, have strengths and weaknesses?
A. Generally speaking, that is true.
Q. That would include even controlled clinical trials. True?
A. Absolutely.
Q. Would you agree scientists often do disagree about the relative strengths and weaknesses -- let's focus on epidemiology studies.
A. I didn't hear the whole question.
Q. Would you agree scientists and epidemiologists often disagree about the relative strengths and weaknesses about epidemiologic studies?
A. I'm sure that happens.
Q. Would you agree that while the Bradford Hill considerations are sometimes called criteria, they are not really criterion in the sense of clicking off boxes?
A. They are often called criteria, and I agree with you that it is not a checklist with boxes.
Q. If I could, I'm going to show you, rather than showing you an exhibit --
MR. TISI: And, your Honor, it is on page 133.
Q. You referred to Dr. Gordis as one of your teachers?

A. That's correct.

MR. TISI: Your Honor, he is one of the editors --

THE COURT: That's okay. I wasn't handed up plaintiffs' book.

(Pause.)

MS. BROWN: Where in the book, counsel?

MR. TISI: It's 133.

Q. He has a chapter on "From Association to Causation Deriving Inferences From Epidemiologic Studies." Do you see that?

A. I do.

Q. This is a chapter you are familiar with. Have you seen this book before?

A. So there are a couple of editions I have seen. I think the Fifth edition. And I have the current one, which is either 2018 or 2019. I don't know how many changes they make from edition to edition, but if this is an edition I have seen, then, yes.

Q. Would you go to page 260. I'm going to ask you if you agree with this, Doctor. It says:

"Although causal guidelines discussed in this chapter are often referred to as criteria, this term does not seem entirely appropriate. Although it may be a desirable goal to place causal inferences on a

firm quantitative and qualitative and structural foundation, at present we do not have all the information needed for doing so."

Do you agree with that?

A. I don't think with that second sentence. This is a conversation we frequently have, is whether to call them criteria. Bradford Hill called them considerations, whatever that means. Criteria is a pretty conventional term. I don't know what's inappropriate about it. It is certainly stuff that epidemiologists talk about all the time.

Q. He goes on to say:

"The preceding list should therefore be considered only guidelines that can be of most value when coupled with reasoned judgment about the entire body of available evidence in making decisions about causation."

Is that true?

A. I agree with it completely.

Q. Does reasoned judgment play a role in deciding whether or not cause and effect takes place?

A. Of course, because it is not a statistical test or something where there is an exact answer.

Q. So scientists can and often do disagree with the ultimate conclusion applying the very same

methodology. True?
A. I don't know how often. You asked me before about individual studies and about disagreeing about the relative importance. I can't speak for everybody, but I can speak for reasonable scientists that I know, and I think if it's a close call maybe people disagree. But I don't think it's just a general proposition it's all over the map.
Q. I'm going to ask you this, Doctor. You understand before your report was issued in February of this year, but after the plaintiffs' reports were due, Health Canada issued a report involving talc and among other things ovarian cancer?
A. I'm aware of that.
Q. The Judge has heard a lot about it, but I would like to spend a little bit of time with it. You read that document?
A. I have.
Q. It is dated December 2018, and it is Exhibit No. 56 in your binder, your Honor. This document is dated December 2018.
A. I don't think I have a 56. I'll follow along with you and maybe find a copy if I need to.
Q. This document -- let's talk about how this document came about, to the best you know, by reading

it.

First of all, when this document came out. You understand Health Canada, first of all, is the Canadian equivalent of the United States Food and Drug Administration. Correct?

A. I don't really know what their role is, and I don't know whether the equivalent of any particular agency. I know they are involved in health issues. But I don't know how they relate to the FDA.

Q. You understand, Doctor, before they issued this particular report, they went ahead and Health Canada asked for a study to be performed by an outside contractor which ultimately became what has been referred to as the Taher analysis.

Do you understand that?

A. Yes.

MR. TISI: The Taher analysis, for the record, is Exhibit No. 63.

Q. If you go to Exhibit No. 63, you go to page -- it was funded by Health Canada. It's right in the back there. Do you see that?

A. I do.

Q. And following that, you understand that Health Canada actually drafted this report. Correct? "This report" being the screening assessment?

A. That's my understanding.
Q. Do you understand this was peer-reviewed?
A. I don't know what process it went through. And we're talking about Health Canada or Taher?
Q. Health Canada?
A. Because Taher has not been peer-reviewed.
Q. If you would go to Health Canada on page 1 of the document.
A. I don't have the document.
(Pause.)
Q. At the very bottom of page 1 it says:
"The human health portion of this assessment has undergone external peer review and/or consultation"? Did you note that when you reviewed this before.
A. I did read that. I just didn't recall it.
Q. The human health portion contains what we understand to be Health Canada's Bradford Hill analysis. Correct?
A. It includes that. That's right.
Q. If you go to the very beginning, you say in your expert report -- on page 49 you say:
"At the end of the day the Health Canada assessment failed to conclude that talc use causes ovarian cancer, and plaintiffs' experts misread the

report to the extent that they said that it did."

See that?

A. I do.

Q. You go on to say at the very beginning of your expert report, it says:

"The assessment by Health Canada and the related analysis by Muhammad Taher and others," you reviewed those documents and you're consistent with the opinions set forth above.

Do you see that?

A. Did you read something else?

Q. On page 47 of your report, you represent the assessment by Health Canada and the related analysis by Muhammad Taher is consistent with the opinions you set forth above. Do you see that?

A. (No response.)

Q. "And they do not support a conclusion that talc causes ovarian cancer."

A. That's correct.

Q. That's not true, is it?

A. It is true. All you have to do, if you read to the end of the Taher article, they arrive at the same place IARC did. They use the same language, and they even evoke IARC by saying the 2010 monograph -- they endorse the exact same conclusion IARC did. It is

absolutely not true they said there is cause.

Q. Would you turn to the Health Canada draft assessment, page Roman numeral III. This is a synopsis of the entire report. Correct?

A. Yes.

Q. We pulled out what it says about their analysis. It says:

"The meta-analyses of available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. Further, available data are indicative of a causal effect."

Do you see that, Doctor?

A. I do.

Q. I assume you disagree with that because in your deposition you called that -- I think the words you said were it was ridiculous?

A. I don't know for a fact it was ridiculous. But the part of the Bradford Hill analysis was ridiculous.

This, by the way, is not the same as saying that they've arrived at a conclusion that talcum powder causes ovarian cancer. If they are assembling data, data could be indicative. Just like we looked at case-control studies, and a case-control study that

has a positive odds ratio is indicative of. But when you summarize all the evidence together, that's a different conclusion. So just to say there is available data is not the same as saying that talcum powder causes ovarian cancer.

Q. Let's look at what they did, Doctor.

Since this is about methodology, let's look at what the methodology they used and see whether or not it tracks the methodology that was used by you and by the plaintiffs' experts in this case.

If you go to page 15 in the section that was peer-reviewed, it talks about "perineal exposure to talc." Do you see that?

A. I'm with you.

Q. This is the section where they start talking about the analysis of the talc data. Correct?

A. That's right.

Q. And they acknowledge the IARC working group, which we will talk about in a moment, in the first paragraph. Right?

A. Acknowledge and recapitulate their conclusion.

Q. As background material. Correct?

A. Correct.

Q. Then they start to review the animal studies. Do you see that?

A. I do.
Q. And they then, the next section, they start talking about the human studies. This is what epidemiologists do. Correct?
A. Human studies?
Q. They looked at the animal studies and they looked at the human studies?
A. Epidemiologists look at the human studies, for sure, if we are talking about the relevant ones. I don't know that epidemiologists do a thorough review of animal studies and may look for a summary. But an epidemiologist will consider animal studies.
Q. Because that bears on the issue of biologic plausibility. Correct?
A. It does.
Q. So in this document Health Canada, after having had an analysis by the outside Taher group, they then write their own report, and in their own report they summarize the human data and the animal data. Correct?
A. That's correct.
Q. You will see table 6-1, which is a chart of many of the different epidemiology studies that you have talked about and Dr. McTiernan talked about. Correct?
A. Correct.

Q. Among the other things they list are the sample size, et cetera. Correct?
A. That's correct.
Q. If you go to page 18, they talk about "mode of action." See that?
A. I do.
Q. I want to pause here a minute and talk about some of the things Health Canada is looking at again only six months ago. Correct?
A. Correct.
Q. This is contemporaneous with what we are doing here today, correct, looking at the data?
A. I guess, yes.
Q. They say:

"With respect to talc specifically, local chronic irritation leading to an inflammatory response is one possible mechanism of tumor progression that is frequently hypothesized. It is known that persistent indications of inflammation, including C-reactive protein, tumour necrosis factor, and other inflammatory markers, are detected in the blood of women prior to a diagnosis of ovarian tumors."

Do you see that?
A. I do.
Q. It goes on at the bottom, the last sentence, it

says:

"There is support for an association of inflammation and increased risk of ovarian cancer," citing the National Academy of Sciences."

Do you see that?

A. I do.

Q. I just want to confirm with you this is what people outside the courtroom -- you understand that Health Canada doesn't have anything to do with this litigation whatsoever. Correct?

A. I think they do now. Dr. McTiernan said they invited her to participate in the process so they are probably somehow linked. Otherwise, I don't know of any links.

Q. At the time of this report you have no evidence that they were involved in this litigation.

A. No, of course not.

Q. They are looking at the data; and if we are trying to assess whether or not the experts in this case are acting reasonably in their interpretation of the data and studies, one of the places we might look is to look at, as you pointed out, what people outside at the courtroom are doing. Correct?

A. It includes that.

Q. One of the things they are looking at here is,

this isn't some harebrained idea that there is inflammation, is a biologically plausible mechanism; this is something that the scientists at Health Canada looked at and assessed and put into their report.

I'm not asking whether they are correct or not correct. I'm asking you whether or not this is the kind of information that experts did outside the courtroom.

A. This was done outside the courtroom. Can you repeat the first part of the question? I lost you by the time we got there.

Q. Doctor, if you would look, this whole discussion of inflammation is something that the scientists in Health Canada were doing independent of what plaintiffs' experts and you were doing when you were preparing your expert report. Correct?

A. Correct.

Q. If we are trying to check whether or not the methodology that was being used by the experts in trying to decide the question whether or not talcum powder products cause ovarian cancer inflammation and this discussion of the studies here are some corroboration of that. True?

A. Oh, my gosh. Some corroboration is very different. This says that local chronic irritation is

a possible mechanism that is frequently hypothesized. Hypothesis is something you serve up in order to test whether it is true or not. So to me to lead in with that really is consistent with all of the uncertainty I have seen expressed by other authors. That's not the same as it's been demonstrated.

Q. Don't they go on and cite studies that support that hypothesis?

A. Sort of. We have Trabert by 2014.

Q. I'm just asking whether they cited articles that support the hypothesis.

A. Yes, indeed.

Q. On the next page they talk about migration. They call it translocation. They talk about different studies that deal with that issue?

A. Correct.

Q. The next paragraph after that they talk about whether or not talc gets to the ovaries via inhalation in the lymph nodes. Correct?

A. Are you saying --

Q. It says."

"Another possible mode of action that is hypothesized in the scientific literature is immune-mediated."

Do you see that?

A. I thought you asked if they said it was by inhalation.
Q. I withdraw that.
The next section here talks about a different mode of action other than migration. Correct?
A. That is correct.
Q. And they provide the support for that. Correct?
A. Correct.
Q. The next one is they talk about the meta-analysis. Correct?
A. Correct.
Q. And in there they talk about the fact that they had gone ahead and contracted a new meta-analysis by Taher. Correct?
A. They do.
Q. And then they go through and they discuss each of the different Bradford Hill criteria. Correct?
A. They do.
Q. Let's take, for example, the strength of association. There is a discussion of that. Correct?
A. A discussion --
Q. Of the strength of association. Correct?
A. That's not a conclusion, though.
Q. I said they discuss it.
A. I understand. It is not the same as doing a

Bradford Hill analysis to discuss it. You actually have to do something with it.

Q. They are considering each and every one of the Bradford Hill criteria in this document. Correct?

A. They do.

Q. The first one they consider is "strength," and they discuss the meta-analyses and what is seen in the meta-analyses. Correct?

A. They include that.

Q. One of the things that they say, and I want to spend a moment with this paragraph on page 20, it says:

"The individual cohort studies did not show a statistically significant association between perineal talc use and ovarian cancer."

Correct?

A. That's correct.

Q. They go on to give reasons why that might have under-estimated the risk. Correct?

A. They give some reasons why that could be.

Q. "However, there was a positive association." See that?

A. In the case-control studies.

Q. No --

A. I'm sorry. With the serous ovarian.

Q. Correct.

(Reading.)

"However, there was a positive association with statistical significance, specific to invasive serous-type ovarian cancer in the cohort studies."

Do you see that?

A. I do.

Q. It says:

"Given the long latency for ovarian cancer, the follow-up periods may not have been sufficient to capture all the cases for the individual cohort studies."

Do you see that?

A. I do.

Q. They are identifying the very same kind of issues that you heard Dr. McTiernan talk about yesterday. Correct?

A. Some of these, yes.

Q. The next thing -- and, of course, as we talked about before, Dr. McTiernan had no involvement in this process of developing this report, to your knowledge?

A. As far as I know, she did not.

Q. The next thing it says:

"Given the rarity of ovarian cancer, many of the available human studies may not be sufficiently

powered to detect a low odds ratio."

Do you see that?

A. I do.

Q. It goes on to say:

"With larger sample sizes, more individual studies may have demonstrated stronger associations."

These are the very kinds of things that Dr. McTiernan and plaintiffs' experts identified totally independent of this analysis. Correct?

A. These are the same things most of the folks involved here have identified. They didn't go out and discover something new. They've assembled some of the same stuff that's out there.

Q. If you go to the Taher report, they also talked about the issue of nondifferential misclassification because the people in the cohort studies, the women in the cohort studies were only interviewed once during the course of the study about their talc use. Do you remember that?

A. Yes. They hypothesized that was a possibility. They didn't demonstrate that was a truth or a fact.

Q. Doctor, you hypothesized recall bias was an issue with these studies, that confounding was an issue with these studies?

A. What's kind of cool, though, is that I actually

showed an exact example from these particular epidemiologic studies which demonstrated it exactly. So it's not just a hypothesis. It's actually a fact based on at least the one study.

Q. What I'm trying to ask you, Doctor, is outside the courtroom the scientists who were looking at the same question you and Dr. McTiernan were looking at were considering the very same kind of issues that you and Dr. McTiernan talked about over the past two days. Correct?

A. Generally speaking, I'd say there is some overlap with at least the content of what these are.

Q. The next issue is on "consistency." You testified there is no consistency. Correct?

A. I did not. I said when you look at the information in total, that it doesn't satisfy the consistency criterion because what I said was including that you are not just looking for a couple of examples where a couple of studies may be consistent with each other, but does the total body of evidence show consistency.

Q. Well, Health Canada addressed that issue, did they not, outside of the courtroom?

A. They did.

Q. They said:

"Several meta-analyses conducted over the past 15 years calculated similar odds ratios and resulted in similar conclusions."

Did I read correctly?

A. You did.

Q. It says:

"There is a small yet consistent and statistically significant increased risk for ovarian cancer with perineal talc use," and cites the very same studies that you and Dr. McTiernan have talked about over the past two days. Correct?

A. Yes.

Q. They go on to say:

"The epidemiological studies examined in these meta-analyses were conducted over different periods of time across more than four decades among different ethnicities and spanned many geographical areas worldwide."

Do you see that?

A. I see it. They don't say whether there is consistency or not. You are exactly right. They are describing the same sorts of things Dr. McTiernan and I considered. But I also evaluated. I don't see an evaluation here whether they are consistent.

Q. Doctor, in fairness, let me ask you this: What

is the importance of replication?
A. In what context?
Q. For epidemiology.
A. It is so abstract, I'm not sure what you mean.
Q. Does Dr. Gordis deal with that issue?
A. I'm sure he probably does.
Q. One of the important things about studies, not when you are looking at an individual studies, but when you are looking at multiple studies, is to see whether or not those studies were conducted in different populations with different researchers in different areas under different conditions using different study designs.
A. Yes.
Q. By doing that, you reduce the issues of confounding, bias, chance. Correct?
A. No, not necessarily. The biases that we're talking about in this case, such as information bias, would function the same way. That's why when you find a very small risk, it is not surprising to find that small risk in different places. So the reason recall bias functions in sick people differently than healthy people, regardless of where they are, and when people are shy or reluctant to talk about something sensitive, that functions across countries as well.

It doesn't necessarily take care of that problem.

And the confounders you still have to assess them and acknowledge them. Just doing studies in multiple countries doesn't take care of confounders if you don't assess the confounders.

Q. Doctor, one of the issues you raised is douching. Correct? Correct?

A. Correct.

Q. Douching was based upon what study?

A. The Gonzalez study.

Q. And the Gonzalez was a United States study?

A. It is.

Q. There were multiple studies conducted around the world, correct, case-control studies?

A. There are a few that were world-wide and most U.S..

Q. There were three studies in Australia, one study in China, one study in Greece, a study in Israel, several studies in Canada. Correct?

A. Correct.

Q. In order to assess that question -- do you know whether or not douching is even something that is a -- in order to be a confounder, douching would have to be associated with the use of talc?

A. If it is going to confound the relationship

between talc and ovarian cancer.

Q. Because confounding doesn't mean confusion. There is a very specific formula or criteria to meet the criteria to be a confounder. Correct?

A. It is definitely not confusion.

Q. It has to be associated with the item under study. Correct?

A. In order to confound the relationship between the exposure and the outcome.

Q. And so when you went and were looking at the issue of douching, did you go and make any effort to see whether or not in the other countries, in Australia where they found statistically significant increased risk in the case-control studies; in China, where there was an increased risk, did you go and see whether or not women douched in connection with the use of talcum powder products?

A. There are a couple of questions. I did look at every single study I had available to me to see whether or not douching was accounted for. There was one case-control study that did account for it, and I think there may be a second I found subsequent to that. That was all that I found.

Separately if there is a relationship between douching and talcum powder use -- they for sure looked

at that in the Gonzalez study. I don't remember whether any of the other studies looked at the concordance of those two habits.

Q. Did you go and see whether or not there was any data in any of the other countries in which douching -- because to be a confounder, it would have to be related to the use of talcum powder and see whether or not there's any use data that would confirm that as a confounder in those countries?

A. I think I just answered you. I said I went and looked at every single study for what they assessed about douching.

I know for sure the Gonzalez study looked at the correspondence of the two habits. Together they had an odds ratio of 2.1 for the relationship between the two of them, and I don't recall whether there was -- there is only one study or two studies at most that even accounted for douching.

Q. That wasn't my question. There are three Australian studies. Correct?

A. I don't remember the count. I believe you.

Q. There were three Australian studies, Purdie, Green, and Merritt, all statistically significant in Australia. Correct?

A. I'm confused by your title.

THE COURT: This is listed as recall bias and not douching. Based on that title, how does he know they are douching?

Q. The studies did not adjust for douching. These three studies did not adjust for douching.

My question is: Do you know whether or not women in Australia even douche?

A. I have no idea.

Q. Do you know whether or not that it is associated with the use of talcum powder products in Australia?

A. No idea.

THE COURT: You are asking about the studies. I would like to move on. You are asking about has he considered studies in this connection. I thought you were pointing these out as ones that considered it. We started with Gonzalez. He said he clearly did. I don't know where we are going with some hypotheticals, whether they do. You don't know either. Maybe you do.

Q. Going back to the Health Canada assessment, if you look at the specificity section, they talk about that. Correct?

A. They do.

Q. They identify specificity, that the cancers are specific to the ovaries as opposed to any other of the

female anatomy. Correct?

A. They've gotten that so incorrect. That's not what specificity means in the Hill criteria.

Q. You may disagree with their assessment but they assessed it. Correct?

A. Well, in a couple of cases I don't see that they assessed to reach a conclusion. They just put down some things they might have considered. In some of these cases they are saying stuff that isn't true. For temporality, that you brought up, you said in all case-control studies, reporting positive outcomes, the participants recalled the exposure to talc preceded the reported outcome. Well, of course, that's true. That's what happens in cross-sections, that you can ask the people about the past. That's not the same as demonstrating temporality. So they've actually reported something here that doesn't show temporality.

It's just like the specificity thing, where they say perineal talc exposure is specifically associated with cancer of the ovary. There has to be a one-to-one association between the exposure and the outcome, generally speaking, which is super rare. This is just a sentence where they have the word "specifically" in it.

Q. Do you disagree with them?

A. I disagree that that particular sentence is supportive of the notion of specificity, even though they've used the English word "specifically" in it.
Q. They also addressed "biological gradient," which is dose-response?
A. Right. They say there is a lack of available exposure effect relationship.
Q. They also say that seven studies provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc, although the evidence wasn't clear. Correct?
A. Yes.
Q. Does the Bradford Hill criteria require that there be consistent statistically significant increased risk for dose-response in order for this criteria to be met?
A. None of the Bradford Hill criteria are required including that one.
Q. "Biological plausibility," do they deal with that issue, the next page? Do they talk about the issue of biological plausibility?
A. Yes.
Q. Do they say, "the presence of talc in the ovaries has been documented"?
A. They do.

Q. "This evidence of retrograde transport supports the biologic plausibility of the association between perineal talc application and ovarian exposure." Correct?
A. They do.
Q. And although they also say that the specific cascade has not been established, you would agree that they do discuss the biologic plausibility of migration as being a mechanism by which talc gets to the ovaries?
A. They do discuss it.
Q. They talk about "coherence" as well. Correct?
A. Yes.
Q. And at the conclusion of all of this, Doctor, they then make another statement that we talked about before from the synopsis. Correct? They say:
"The most recent meta-analysis detailed above, Taher 2018, and consistent with the Hill criteria, suggests a small but consistent statistically significant positive association between ovarian cancer and perineal exposure to talc. Further, available data are indicative of a causal effect."
Do they say that?
A. They do.
Q. They go on to say later on -- if you go to page

27, they repeat this statement, if you go to the middle of the page, it says:

"Data from published meta-analyses of epidemiological studies indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer."

Do you see that?

A. I do.

Q. They quote another article which you are familiar with; it says:

"It is unlikely that the association between talc and ovarian cancer is due to confounding, and so it is fair to say that there is a statistically robust relationship between talc use and ovarian cancer, it is likely to be causal."

MS. BROWN: Counsel, I think you read that incorrectly.

Q. It says:

"It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer, it is likely to be causal."

Do you see that?

A. I do.

Q. And so outside the courtroom, separate and apart from litigation, Health Canada did three things: First, it commissioned the Taher study?
A. Correct.
Q. Second, it wrote a report?
A. A draft report.
Q. Third, it had that draft report peer-reviewed?
A. Somehow.
Q. And, fourth, it published it. Correct?
A. I don't know what "published" means. It's available.
Q. Made it available?
A. Yes.
Q. If you go back to page 27 of the assessment, after the sentence I read below, it says:

"Similarly, Penninkilampi and Eslick noted the confirmation of an association in cohort studies between perineal talc use and serious invasive ovarian cancer is suggestive of a causal association."

See that?

A. I would call it serous probably rather than serious just so that it's correct.
Q. That is the sentence we read before from the Penninkilampi study?
A. Yes, it's the same one.

Q. "Taher and colleagues noted that consistent with previous evaluations by the International Agency for Research on Cancer 2010, and more recent and subsequent evaluations by individual investigators, the present comprehensive evaluation of all currently available relevant data indicates that perineal exposure to talc is a possible cause of ovarian cancer in humans."

Correct?

A. Did they say that? Yes --

MS. BROWN: Can he be permitted to finish his answer?

MR. TISI: I just asked whether it says that.

THE COURT: Well, these are quoting. So we have to be clear. It is the article, whatever this is, the draft screening report, quoting these various sources you've already discussed. It is not the language of the Canadian people. It is their quotes from these articles.

MR. TISI: Correct.

THE COURT: Now, we can continue.

MS. BROWN: Thank you.

THE COURT: Can I just ask, and maybe there is not an answer any of you can give me, but is there anywhere that reflects what the peer review was of

this Canadian report?

MR. TISI: I just have what you have, your Honor.

THE COURT: All right.

BY MR. TISI:

Q. The next thing I want to do is I want to go to the Taher paper. Do you have that in front of you?

A. Not anymore. Is it in this binder?

MS. PARFITT: It is number 63.

THE WITNESS: Thank you.

Q. On page 43 -- and this is outside of litigation. You have no reason to believe that any of the Taher authors have anything to do with this litigation. Correct?

MS. BROWN: Objection, your Honor. It calls for him to speculate. How would he know either way? It may very well have been funded by plaintiffs' lawyers.

MR. TISI: It is not funded by plaintiffs' lawyers.

THE COURT: I understand your representation. The question is: Do you know if the Taher report was funded by any plaintiffs' lawyers?

THE WITNESS: I'm not aware of that.

BY MR. TISI:

Q. On page 43, the authors talk about the cohort studies. Correct?
A. They do.
Q. On page 43 they discuss three of the issues you talked about before with respect to the talc studies, do they not?
A. Are there three? I don't know.
Q. The first one they talk about is latency. Do you see that?
A. Yes.
Q. (Reading.)

"Although cohort study designs are efficient for examining diseases with a long latency period, it is essential that the period between talc exposure and the cancer diagnosis be sufficiently long."

See that?

A. I do.
Q. And they identify the cohort studies may not be long enough to truly identify ovarian cancer related to talc, do they not?
A. So --
Q. I'm asking whether they identify that as a potential weakness of the cohort studies outside of litigation.
A. They are talking about latency here, and they

are talking about latency. I agree with you.
Q. One of the things counsel asked you before is whether or not in assessing epidemiology studies, in your experience, whether or not there is anything different between cancer and the study of any other kind of disease. Do you remember that?
A. Who asked that?
Q. Counsel for Johnson & Johnson.
A. Today?
Q. Yes.
A. Really?
Q. Asked you with your qualifications.
Do you remember earlier on you were asked a question about your qualifications, whether or not your qualifications -- somebody with training in epidemiology, who is primarily a pulmonary physician, whether or not that allows you to analyze studies on cancer? Do you remember that question?
A. Not exactly. But I can answer it again if that's is helpful.
Q. I'm asking you this: Do you know what the latency period is for ovarian cancer?
A. From what?
Q. I'm asking you.
A. I know, but it's an incomplete question. If you

ask, What's the latency for lung cancer?, you have to know what the exposure is you are talking about. If you ask, What's the latency for mesothelioma?, you have to know what it is you are talking about because the latency differs depending upon which exposure.

Q. Have you done research into that?

A. Research in the sense that I've looked to find whether or not there is a known latency period between talcum powder and ovarian cancer, and there is not.

Q. And whether or not these studies are long enough to actually capture that risk?

A. They do seem to be long enough in general.

You are highlighting the Gonzalez study right there. All of these studies have older women, and they are describing something that's a habit. When they ask them about talcum powder, it wouldn't have been just on the day they asked them the question. They are documenting a habit as opposed to just a one-time event.

The Gonzalez study also asked about pre-pubertal girls also, and so they have evidence going back that many decades. These are mature women that were enrolled in the study. So they actually have that kind of time.

What I would say too because you showed me

Narod before, and Narod said we would need 200,000 women followed for 10 years, and with all three of these studies, you have 200,000 women who were already followed for 12 years, and of the other ones was an average of eight years. So you are getting awfully close to the right amount of time, according to Narod.

One of the studies asked about talcum powder use in the 20 years prior to the study. I don't think you can sort of say in general there is not enough time that's gone by. And that's even assuming you knew, which I don't know how anybody could know, what the latency period is between talcum powder and ovarian cancer.

Q. One of the advantages of a case-control study is you can interview people after the fact and find out when their exposure began?

A. You can hope to. But that's the disadvantages, that's it's a hope to, because --

Q. Doctor, one of the advantages of a case-control study is you can interview women about their use looking backwards. Correct?

A. You can interview them, yes.

Q. And you can try and get information as best you can about when they started to be exposed to the issue at interest?

A. You can try to.
Q. You can't really do that in a cohort study, can you?
A. You do that because you are assessing the people at some certain baseline, and you can also ask questions of the women at baseline.

The same question is available to a person who is enrolling in a cohort study as in a case-control study.

Just to be clear. You can ask a woman who is enrolling in either type of study, What were your habits last week? 10 years ago? 20 years ago? That question can be asked in any study design.
Q. So getting back to my original question, the issue of latency is an issue that was raised outside of litigation in this study. Correct? The issue of whether or not the cohort studies were long enough was addressed outside of the courtroom.
A. That is correct.
Q. That is an issue both you and Dr. McTiernan addressed in your reports?
A. That is correct.
Q. You have a disagreement?
A. I don't remember what she says about latency. If it's other than what I said, then I disagree with

her.
Q. The next one is under power. Do you see the next sentence? This is the issue you were just talking about as to whether or not the cohort studies were large enough. Correct?
A. Large enough to what?
Q. Large enough to detect an association.
A. That's where there is a mistake. Any size study can detect an association. But if we are talking about power, we are talking about something different.
Q. But the issue of whether or not these studies were adequately powered to detect an association is an issue that was raised outside of litigation. Correct?
A. Absolutely.
Q. And it's an issue you have addressed in your report. Correct?
A. Correct.
Q. And it's an issue Dr. McTiernan and plaintiffs' other experts addressed in their reports. Correct?
A. That's correct.
Q. And it's an area upon which you disagree. Correct?
A. Yes.
Q. Next page, page 44, they talk about the issue of nondifferential misclassification. Correct?

A. They do.
Q. Remind us again what nondifferential classification is?
A. It's a broad category of whether people are assigned to the wrong exposure but without there being information that drives that; meaning that it's sort of like a random or a haphazard kind of relationship as opposed to it being determined by something in particular.
Q. It's an information bias. Correct?
A. It functions as an information bias.
Q. And if you have nondifferential misclassification unlike recall bias which can be an exaggerated effect, nondifferential misclassification is a bias that can attenuate an effect?
A. Absolutely.
Q. It's something you noted in your literature as well. Correct?
A. What's my literature?
Q. In your cohort studies there is always an issue you have to consider of nondifferential misclassification?
A. Sure.
Q. And that's one of the issues that's being addressed here, whether or not assessing women at one

time in the cohort studies about their exposure to either talc or powders is sufficient to, has a potential of introducing nondifferential misclassification?

A. Correct.

Q. That's an issue that was identified outside the courtroom. Correct?

A. Correct.

Q. It was addressed by you in your report. Correct?

A. Correct.

Q. It was addressed by Dr. McTiernan and Dr. Siemiatycki. It was addressed by Dr. Moorman. Correct?

A. Correct.

Q. It was addressed Dr. Singh. Correct?

A. I'm sure, but I don't remember.

Q. It was addressed by Dr. Smith-Bindman?

A. Yes.

Q. And it's an area where you all addressed it and you have a disagreement. Correct?

A. What's the disagreement?

Q. About the effect of nondifferential misclassification in the cohort studies?

A. What the effect of it is? I don't think I

disagree with how it works.
Q. I'm asking whether it was assessed by all the experts in this case?
A. Yes, it was.
Q. This wasn't a situation where people were ignoring the potential of this bias?
A. Nobody was ignoring bias or confounding or chance.
Q. And so what I'm trying to ask you, Doctor, is both the Health Canada assessment and the Taher assessment were doing in parallel what you and I are doing here today; they were trying to make sense of the data and trying to see whether or not using the Bradford Hill criteria there was a cause and effect. Correct?
A. Taher was a meta-analysis. They did comment on cause and effect, and I think the draft Health Canada document is also trying to consider whether there is cause and effect.
Q. So my question to you is, Doctor, totally separate from being involved in this litigation in this courtroom, in this courthouse in Trenton, New Jersey, people were doing the very same kind of analysis that you and Dr. McTiernan were talking about the past two days?

A. I don't think it's the exact same one.
Q. I didn't say the exact same.
A. I thought I heard you say exact same.
THE COURT: It was very same.
Q. They were doing a Bradford Hill analysis of the available data looking at the very same studies that we have all been talking about. Correct?
A. No. They evoked the term Bradford Hill analysis, and they didn't uniformly do a Bradford Hill analysis. That's when we looked at some of those criteria you asked me to looked at, did they discuss it? Yes, they discussed it, but that is not the same as analyzing it.
Q. Doctor, outside the courtroom, totally separate from what we are doing here, they analyzed, assessed the very data that we have been talking about -- Penninkilampi, Eslick, case-controls, the cohorts -- they are all here. Correct?
A. I think you just twisted back what I just said because I don't think in some cases they did assess. They acknowledged certain things, but they didn't always reach an assessment.
Q. How do you know that?
A. I read it. That's what I'm saying. The point I where I was asking -- am I allowed to comment? And

you said, no. You're just reading it. So we're just reading stuff in. One of my comments would have been is they just listed some things there, but they haven't reached a conclusion. Under strength of association they don't declare whether it's weak or strong as an example. So --

Q. Can you tell us but --

MS. BROWN: Can he be allowed to finish his answer before counsel asks another question?

THE COURT: Fine.

A. It's not enough to just say Bradford Hill, those headings, and then fill in some stuff underneath. You actually have to analyze it. And I'm saying based on what I read, they didn't uniformly do that.

Q. Let's move on.

THE COURT: Perhaps now is a good time to break for lunch, 12:30.

MR. TISI: Yes.

THE COURT: Basically, you used an hour and 15 minutes. So you still have the bulk of your time left.

THE DEPUTY CLERK: All rise.

(Luncheon recess.)

**A F T E R N O O N  S E S S I O N**

(In open court.)

THE DEPUTY CLERK: All rise.

THE COURT: Thank you.

**GREGORY B. DIETTE,** resumed.

CROSS-EXAMINATION

BY MR. TISI:

Q. I want to back up a little bit. Let's see if we can get some things out of the way.

First of all, I want to ask you a little bit about your qualifications and then I'm going to talk about your methodology. So let me ask you a couple of questions right off of the bat.

You are not an oncologist. Correct?

A. Correct.

Q. You are Board Certified in pulmonology?

A. Pulmonology and internal medicine.

Q. There are people who actually do -- people who are oncologists and people who do cancer research as their primary focus of what they do. Correct?

A. That's correct.

Q. You are not one of those people?

A. I am not an oncologist, and that's my not my primary focus.
Q. Your research activities have not been focused on researching causes of cancer?
A. Not focused for sure. I've had some studies that pertained to cancer, but it has not been a focus.
Q. Your focus is pulmonary diseases, things like asthma, those kinds of things?
A. More environmentally caused diseases in general, including asthma, COPD, and other lung diseases.
Q. And there are people actually at Johns Hopkins who actually specialize in cancer epidemiology. True?
A. There have been. I assume there are. I don't know who they are at the moment.
Q. But people wouldn't, when they come to Johns Hopkins, say: I need a cancer epidemiologist; they typically wouldn't say I need to speak to you. Is that fair?
A. If somebody needed an epidemiologist, they might come to me. I honestly don't know what happens if somebody says: I want a cancer epidemiologist. I guess that's what I could say.
Q. Now, counsel provided some slides here about your background and research. Is any of that related to cancer or ovarian cancer?

A. So the clinical work -- I'll start there. That's the part that slipped off the page there. So my clinical work includes training in cancer care as an internist; and one of my responsibilities in the hospital is to work in our oncology center. There's only people with cancer there. So cancer care is throughout the whole enterprise in a way. So I'll see people with cancer on the pulmonary service, on the internal medicine service. There are people with cancer in my clinic.

The other issues are in terms of my degree, part of that included studying cancer epidemiology as part of the clinical epidemiology degree that led me being a professor eventually of epidemiology, and the teaching I do has included teaching of oncologists and other folks who do that sort of research.

Q. When Hopkins University puts information out about you, it does not indicate that your research interest primarily is cancer. True?

A. You know, I think either your colleague maybe showed me something from our website. I don't know for the most part what my university puts out about me. There are a couple of websites out there that it seems as if only lawyers seem to care about. I don't know what else gets out there.

Q. This indicates your background as a professor of medicine -- I'm sorry -- and expertise and research interests?

Johns Hopkins University has Greg Diette, and it has your expertise as asthma, chronic obstructive pulmonary diseases, critical care medicine, pulmonary medicine, and it actually indicates your research interests are environmental impacts on lung disease. Is that correct?

A. That's what it says, yes.

Q. And epidemiology of airway disease?

A. Correct.

Q. And chronic obstructive pulmonary disease and asthma. Correct?

A. Correct.

Q. Your CV is in the record. That is really a good summary of your primary focus of your professional career?

A. I wouldn't limit it to that. I don't know what website that is and why it was so succinct, but those things are all true about me.

THE COURT: At the top corner it said "Find an Expert?"

THE WITNESS: I didn't populate it. Nobody asked me to contribute to that. If it's a way to find

a clinical doctor, there are some sites where there just was two or three bullets about reasons why somebody might come to the doctor. Anyway, it's nowhere near complete. Somebody just populated that.

Q. Doctor, how many of your articles deal with risk factors for gynecologic cancer?

A. Zero.

Q. How many people with ovarian cancer?

A. Zero.

Q. You have been an expert in many cases. Correct? How many cases this past year, past 12 months.

A. Probably about 15 cases, I'd say.

Q. You indicate this is 20 percent of your total time. That's not 20 percent of your professional time. It's 20 percent of your time period. Correct?

A. 20 percent of the time I do some work.

Q. You have testified primarily on issues relating to lung disease. Correct?

A. Correct.

Q. You are involved in several cases -- putting this case aside -- several cases involving mesothelioma and exposure to talc?

A. I don't disagree there have been cases with lung disease. I don't know if "primarily" is right. Certainly, there are lung disease cases.

Q. Well, let me step back a bit and ask you this directly, Doctor: The issue we talked about, the first observational study of ovarian cancer happened in 1982. From 1982 to now, has Johnson & Johnson or any talc manufacturer ever come to you and said: Dr. Diette, I really need your opinion on whether or not talc causes ovarian cancer?

A. No.

Q. Even until today, Health Canada came out with the recommendations we've talked about before, they had a comment period where they could have people come in and give comments. Do you understand that to be true?

A. I understand it because your colleague told me that.

Q. You thought that this was such a sloppy work. Did you ever take the time, given what you have done, to write a letter and a comment to Health Canada to say: You know something? You got it all wrong. This is how you are supposed to look at this question.

MS. BROWN: Your Honor, I would object to counsel's character of Dr. Diette's testimony. He didn't testify it was sloppy work. I think he has some critiques of their process, but I would object to that characterization.

MR. TISI: Actually, your Honor, he did at his deposition, and I can show him. It takes about 5 seconds.

THE COURT: It doesn't really matter the words being used. The real question is, you clearly disagreed with some of the things they did in their methods. Did you ever write a letter?

THE WITNESS: Other than this matter, I don't even know who Health Canada is. It is not part of my business to write them letters about anything, including this.

BY MR. TISI:

Q. It is part of your business to be an expert. Correct?

A. In this particular matter. But I honestly don't know Health Canada. I've never looked up something about Health Canada.

Q. That's interesting, Doctor, because let me ask you this: Health Canada -- did J&J ever say -- not J&J's lawyers. J&J the company. Did any scientist at J&J come to you and say: You know, we have this comment, period. We need to write to Health Canada and tell them why they are wrong about their draft health assessment. Did anybody come to you from the company and say: Dr. Diette, can you please help us

draft something to send to Health Canada, because they got it all wrong?

A. No.

Q. Have you ever sought beyond the confines of this expert report, or whatever expert reports you did in litigation, to tell people about your opinions of your colleagues, your professional colleagues, your regulators, about your views of ovarian cancer and the talc issue?

A. Professional colleagues I've talked to.

Q. Did you ever present to anybody, Grand Rounds, or anything related to this issue?

A. I have not given Grand Rounds on this issue.

Q. Have you ever given a PowerPoint or a talk about or anything about ovarian cancer and the risks and any of the opinions you are prepared to give today?

A. No.

Q. Let's talk about some basic issues here.

Counsel asked you some questions about hierarchy of evidence. Do you remember those questions?

A. I do.

Q. I was a little surprised counsel gave you the Gordis text because I was going to give you the Gordis text.

You cite the Gordis text for the proposition that cohort studies are better than case-control studies, and there is a hierarchy of evidence. Is that true?

A. I wouldn't agree with "better". I can clarify my thinking about hierarchy, but I can also wait for your next question.

Q. Keep going.

A. When we are talking about a hierarchy of evidence, it exists in terms of the clinical studies, and there are strata. For example, clinical trials are considered among the highest quality or highest tier of studies, the observational studies that are cohort and case-control belong together, and beneath those are case reports and case series.

But even within those strata you can still sort. So there are different kinds of clinical trials. And so within clinical trials, there are different types of clinical trials. So you would place a randomized control trial above a nonrandomized control trial. And even within that band where you say clinical trials are higher up than say observational studies, they are still within that band of the hierarchy. And so when you get down to observational studies, generally speaking, cohorts get

the nod over case-control, but they do belong in the same strata.

Q. They do belong in the same strata and in fact Dr. Gordis says they belong in the same strata, don't they?

A. I'm sure he said something approximately like that.

Q. So when counsel put this particular slide up, nothing in this slide says that cohort studies are more reliable than case-control studies; they just say typically they come first. Right?

A. If you read it and try to understand it, I think you will get that, though, because what this says is a case-control study is useful as a first step. But if that's all you needed, it wouldn't say the next step is to carry out a cohort study.

So the point here is that there is something about the cohort study that adds value even when you have information from the case-control study, and that's exactly what that so-called real world example shows, is that there is something to do next.

Q. The real world is that case-control studies are easier to do, they are easier to do, they are less expensive, and that's why there are more of them. Correct?

A. On average, they are less expensive. They are certainly more feasible to do time-wise in most cases. Whether there's more of them, I don't know. In this matter, that might well be why. But I don't know in general for the world how they compare.

Q. So if scientists are trying to discover an association or not, the first step is because of expense and ease is to do a case-control study. Correct?

A. Yes. Just to dial it back, the first step would be to report a case or a case series to make the observation and then to try to follow that up with what's next, and it could be either a case-control study or a cohort. It often is a case-control if that's the feasible one to do.

Q. Let's look at what Dr. Gordis actually says about case-control and cohort studies.

I have another copy of Dr. Gordis' text. Do you have that up there, Doctor?

A. I did not bring his text with me.

Q. On page 257 of his textbook, he has an example of how you look at studies; does he not?

A. We're talking about Table 14-3, which is "The Process For Using the Evidence and Developing Recommendations on the Effectiveness of Prenatal

Interventions."
Q. Correct?
MR. TISI: Your Honor, for the record, this is in your book at plaintiffs' opposition Exhibit 133.
THE COURT: Thank you.
Q. If you go to the next page, Doctor, he talks about this as an example. He says:
"They thus defined an approach for looking at causation that may have applicability far beyond questions of effectiveness of prenatal measures."
Do you see that?
A. I don't.
Q. Do you see that, Doctor?
A. I don't know what that sentence means all by itself. What's they? It says, they thus define --
Q. "They" -- the people who have drafted the process for using evidence to develop recommendations on prenatal interventions.
A. Okay.
Q. If you go to this Stage I, and this is really useful because I think it illustrates what we have been talking here.
If you go to Table 14-3, the first step is "Categorizing Evidence By Quality and Source."
Do you see that?

A. I do.
Q. And the first is "Trials," and you talked about that. Correct?
A. I did.
Q. But even trials can be badly done. Correct?
A. Oh, any study can be badly done.
Q. So you have to look at the trials. You can't just throw it in a category because it says "randomized clinical trial" in front of it. Correct?
A. Of course.
Q. The second is, "Cohort or Case-Control Studies." Correct?
A. Yes.
Q. Underneath it talks about different aspects of studies that can affect their quality. Correct?
A. Sure.
Q. At the very bottom it says:
"Among other issues that must be considered in reviewing the evidence are precision of the definition of the outcome being measured, the degree to which the study methodology has been described, adequacy of the sample size, and the degree to which the characteristics of the population studied and of the intervention being evaluated have been described."
Correct?

A. That's correct.
Q. The concept they are trying to get through here is you don't simply put things in a hierarchy because there is some formula. You have to look at the attributes of each study and how they were conducted and whether they were appropriate to answer the question. Correct?
A. Of course.
Q. So anybody who would come into court and simply say, We have a pyramid or a hierarchy, where we put cohorts above case-control, above case series, above individual case reports, anybody who does that mechanically isn't doing their job as an epidemiologist. Correct?
A. You are absolutely incorrect. This is one table. This doesn't help to define the entire universe of what my profession does, and I think invariably clinical trials, as you said, are the highest tier of evidence, and there's a reason we use them that way.

What you are also saying is that there are quality issues, which I agree with, that allows the clinical trial may not inform you as well as a really good cohort because you may get better data from the good quality study.

Generally speaking, they belong in some order as you evaluate them. That was the point of the earlier quote from the same textbook, which is talking about the sequence of doing studies, that you confirm what you think you learn from the case control or the cohort. The next step after that is a clinical trial, if you can do it. So there is a sequence that makes sense.

Q. Doctor, you indicated in your expert report -- I'm reading from it, on page 5 -- "cohort studies are widely regarded as more reliable." You cite Gordis. There is nowhere in the Gordis text that says that. Is that true?

A. I didn't quote him.

Q. You did quote him. Actually, if you look at your footnote here, it goes to footnote 3 of your report, you cite generally Leon Gordis epidemiology without a page, footnote 5 on page 5.

A. I think you are confirming what I just said. I didn't provide a quote. My interpretation from having this textbook and having been taught from it, different versions, and using it, is that what I said is correct.

Q. Doctor, in this big textbook, if this was such a fundamental principal in this big textbook you used at

Johns Hopkins and cited in the Judicial Manual of Scientific Evidence, if this was a fundamental principle of epidemiology, don't you think Dr. Gordis would say that?

A. I have no idea what he would have said. I'm embarrassed we are even having this conversation because this so baked in what I do for a living, and what I was taught, and what I teach other people, that it's not the kind of thing I usually provide a citation for.

Q. Being baked in --

THE COURT: There is no quote. I'm not sure what you were saying.

MR. TISI: Well, he's citing to the sentence as a proposition -- he's citing the proposition there is a hierarchy of evidence --

THE COURT: You said it was in quotes. He is not quoting anything. I want the record to be correct.

MR. TISI: No quotes, your Honor. The principle --

THE COURT: Let's move on.

Q. The next thing I would like to do -- would you please bring up misconception.

Since this is baked in, and you are

embarrassed we are having this conversation, do you know who Ken Rothman is?

A. I know of him. I don't know him personally.

Q. You are a peer reviewer for the journal Epidemiology?

A. Yes.

Q. Do you know Dr. Rothman founded the journal Epidemiology and was its editor for many years before he retired from it?

A. I do not.

Q. Do you know that his textbook is widely used and cited in the Judicial Manual of Scientific Evidence?

A. I don't know what that is.

Q. I'm going to show you what has been marked as Exhibit No. 58. It is an article titled, "Six Persistent Misconceptions."

You have seen this article before. Right?

A. I think your colleague showed it to me.

Q. Misconception No. 1, could you read it, please?

A. (Reading.)

"There is a hierarchy of study designs, randomized trials provide the greatest validity, followed by cohort studies with case-controls being least reliable."

Q. And if you go down three paragraphs to the very

bottom he discusses the issue of case-controls and cohorts. Do you see that?
A. Yes. But you skipped some stuff that would be important in order to understand that particular statement.
Q. The stuff that's above deals with randomized control trials. Correct?
A. The statement also deals with randomized control trials.
Q. I'm going down to the part that deals with case-control and cohort studies. It says:
"Trials are far from perfect. Furthermore, both cohort and case-control studies will yield valid results when properly designed and carried out."
Do you see that?
A. Yes.
Q. Do you agree with that?
A. Yes.
Q. If you go down to the left-hand column, it says:
"Properly designed case-control studies will produce the same results as properly designed cohort studies. When conflicts arise, they should stem from problems with either or both studies."
Do you see that?
A. I do.

Q. He doesn't say if conflicts arise, choose the cohort?

A. You should look at the studies entirely.

Q. Exactly. Next quote.

"Although case-control studies have long been disparaged as being backwards versions of cohort studies, starting from disease and tracing back to possible causes, epidemiologists today understand case-control studies to be conceptually identical to cohort studies, apart from the efficiency gained that comes from sampling the denominators rather than conducting a complete census."

Did I read that correctly?

A. You did.

Q. So while you might be embarrassed we are having this conversation, the idea that you don't simply elevate cohort studies above case-control studies is in the epidemiology methods literature. Correct?

A. You used a key word which is "simply." I agree with all the other propositions you put forth which is you actually have to look at the studies and the quality of the study. So even if you insisted the case-control studies and cohorts are exactly on the same plane, it wouldn't change any of my opinions about this matter.

Q. Next concept is statistical significance. We talked about that a bit, and let's talk about it again. I would like to go to Dr. Rothman's textbook on epidemiology.

MR. TISI: Your Honor, it is Plaintiffs' Exhibit 20.

Q. This is Chapter 2 of the book entitled, "Causation and Causal Inference." Correct?

A. I don't know. I'm looking at something else.

Q. It is in your binder, sir. The title is "Modern Epidemiology." The copy of the book is right here. "Modern Epidemiology."

MR. TISI: Your Honor, for the record, it is cited in the "Judicial Manual for Scientific Evidence" as one of the references, and that is on Diette Exhibit 1 -- it is Opposition Exhibit 20.

THE COURT: I hope you have permission to copy the chapter. There is copyright. I'm just noting that.

MR. TISI: Since I'm defending Dr. Rothman --

MS. BROWN: Could we make sure Dr. Diette has a copy of it.

THE WITNESS: I have it now.

BY MR. TISI:

Q. If you go to Chapter 2 entitled, "Causation and

Causal Inference," 27, he says -- this is under the consistency prong of the Bradford Hill criteria. Am I correct?

THE COURT: What page did you say?

MR. TISI: 27.

Q. Just to orient ourselves, this discusses the Bradford Hill criteria and how it is taught to epidemiology students. Correct?

A. What it says in this book?

Q. Yes. It says "causal criteria" on page 26. The first category is "strength"; the second category is "consistency"?

A. In terms of getting me to agree with what you are saying, I don't doubt there are students that use this. When I took the case-control study course at Johns Hopkins we used the book called Schlesselman. So we didn't use this book. I don't know why. I don't know whether other people use it or not, but it's not the book I used.

Q. On page 27, under the consistency prong, second paragraph, Dr. Rothman and his colleague, Dr. Greenland said:

"One mistake in implementing the consistency criterion is so common that it deserves special mention. It's sometimes claimed a literature or set

of results is inconsistent simply because some results are statistically significant and some are not. This sort of evaluation is completely fallacious even if one accepts the use of significance testing methods."

Do you see that?

A. I do.

Q. Do you agree with that?

A. I believe we talked about this in my deposition, that it says that if you do that it says some results are statistically significant and some are not. I agree. If that's all you did was line things up and say these are and these are not, and that's simply what you did, you would not be done with your analysis, and I agree with that.

Q. So if anybody had done a methodology and simply sorted by statistical significance and put them in one bucket on one hand, and nonsignificant results in another bucket, and then sorted by study design, that would not be proper methodology. Correct?

A. Incorrect. Sorting them into buckets is not the problem. If we're going to read what he says, he says to simply do that is a fallacy or it's fallacious. I agree with that. If you do that and you stop there -- look at the Taher study; they count up how many studies are statistically significant or not, and they

don't stop there either. They are not wrong to describe the studies as being statistically significant or not. They would be wrong if they only did that. That's how I read this.

Q. The way you read it is in the context in which it is written. It is written under the section involving consistency of association. Correct?

A. I'm reading this under the context of how it is written? Well, of course.

Q. It is written in the section that deals with consistency. Correct?

A. Exactly.

Q. And so what we're trying to figure out, are studies consistent. Correct?

A. Are studies consistent?

Q. Yes, are multiple studies, when you line them up, are they consistent?

A. It says that if you simply do that, that you have done something wrong.

Q. And do you agree with that?

A. If that's all you do.

Q. The next thing I want is to show you another textbook from Dr. Oleckno, and that is Opposition Exhibit 1, 43. I would ask you to go to page 222.

MS. BROWN: Counsel, is that in the binder you

gave me?

MR. TISI: It is in the binder. It is Exhibit 143.

Q. On the left side on page 222 it says the following:

"Finally, statistically significant is often misinterpreted as meaning that the null hypothesis is false or that the association is one of cause and effect. Neither can be demonstrated using statistical significance testing, which depends on probabilities. For these and other reasons most epidemiologists prefer to use confidence intervals."

Do you see that?

A. I do.

Q. Do you agree with it?

A. I'm still trying to figure out what this is. I don't know who Oleckno is.

Q. Your colleague, Dr. Merlo, who is also an expert in this case relied on this textbook. You know who Dr. Merlo is. Right?

A. I do.

Q. Dr. Merlo, who is one of the other epidemiology experts whose opinions they are challenging, has relied on this textbook.

A. I don't doubt you. I just don't have any idea

who this is.

Q. Well, do you agree with the principle most epidemiologists look to confidence intervals rather than just simply deciding whether or not something is statistically significant or not?

A. So I think most epidemiologists look at both of those things, but you have to understand that they are complimentary. It's not as if one versus the other. A 95 percent confidence interval is the equivalent of establishing what a P of less than .05 is.

I think the way I have been hearing the conversations go about this matter, there seems to be some confusion about that. But if the P is less than .05, the 95 percent confidence interval is going to include 1. So they are basically redundant in one way, but they tell you some complimentary information about the significance.

Q. So you look at it all?

A. Of course.

Q. When Dr. McTiernan was here yesterday, one of the things she said was that you just don't simply look at whether or not the lower bounds of the confidence interval crosses 1. She says you look at it all. You look at where the confidence intervals -- how tight they are, where the point estimates are, and

how they line up. You remember that testimony. Correct?
A. I do.
Q. That's the way epidemiologists look at it. Correct?
A. You look at all of those things. That doesn't mean you can reach the conclusion that you are going to reach just by doing that.
Q. What you don't do is, you don't ignore everything that happens on the right-hand side of the null value and only see are there studies that cross 1 and then collapse it to only deal with the cohort study?
A. I think in almost any question you asked, if you say you only do something, I'm going to disagree with you. If you say you do something, I may well agree with you. You certainly may look at whether or not the confidence interval includes 1, and you should use that to inform something about what the information is telling you. You should also do what you said which is to also look at the confidence interval and how wide it is. Those are both things that you do.
Q. At the end of the day, one of the things you have to do is you exercise your professional judgment to try to decide what this all means. Correct?

A. Yes, although there is not information enough information on that particular slide to reach the conclusion whether or not there is causation.

Q. I didn't say that, Doctor. We're talking about it in context of consistency of association. One of the things we talked about is: Are these results consistent? What you don't do is you don't block off what is to the right of the null value and then sort them by study design.

A. I agree that you don't simply do that. Each time you say "only" it suggests something. But if all of those values that we saw on that forest plot were all well to the right of the line of unity, that one line, that would tell us something. If they were all completely to the left, that would tell us something. If there is a mixture, that tells us something. So you do look at it. But how you reach your conclusion about causation doesn't come from just looking at that.

Q. But one of the things you have to do when you do look at this is to exercise your judgment and try to decide what this all means?

A. That's part of the picture.

Q. Now, the other thing you said, and you asked and I wrote this down when J&J's lawyer asked you, you

said confidence interval crosses 1 means no association. Is that true?

A. That's what we were reading from that article.

Q. But that is not true, is it? When it crosses 1, you can't make any decision about association. Correct?

A. Incorrect. That's why I brought that article, because it comes from a current good journal, from the Nurses' Health Study, and because those authors used the conventions that those of us who publish papers and write grants have to use when we communicate with people.

Q. Doctor, let me bring up Exhibit 142, please.

Are you familiar with the American Statistical Association?

A. Barely. I've heard of them, and I've heard the most I've ever heard in my life from you guys.

Q. Do you know whether or not Dr. Ballman was an officer -- one of your co-experts for J&J was an officer of the American Statistical Association?

A. I don't know.

Q. Let me see if we could go to the next page.

It is the American Statistical Association's statement on p-Values, Content, Process and Purpose.

Do you see that?

A. Yes.
Q. One of the things -- I want to go through this very briefly.
On the left-hand side at the bottom it says:
"The ASA Board decided to take up the challenge of developing a policy statement on p-Values and statistical significance, it did so recognizing this was not a lightly taken step."
Do you see it?
A. I do.
Q. First of all, you are not a statistician or biostatistician; are you?
A. I don't hold myself out that way, but biostatistics is part of my training and part of the tool set that I use in my work.
Q. Next column, second paragraph, this is by contrast:
"The Board envisioned that the ASA statement on p-Values and statistical significance would shed light on an aspect of our field that is too often misunderstood and misused in the broader research community and in the process provides the community a service."
Do you see that?
A. I do.

Q. (Reading.)

"The intended audience would be researchers, practitioners, and science writers who are not primarily statisticians. Thus, this statement would be quite different from anything previously attempted."

Do you see that?

A. I do.

Q. This was the first and only time the American Statistical Association ever took the step to make a comment on a statistical matter.

Do you understand that to be true?

A. I don't know. It's interesting.

Q. Next page.

"The people who are involved in this process" -- if you go on the left-hand side.

Do you know who Jim Berger is and Steve Goodman?

A. I know Steve Goodman.

Q. He is at Johns Hopkins; isn't he?

A. Not anymore.

Q. Was he?

A. He was.

Q. Good researcher?

A. Yes. I think so.

Q. Now, one of the things attached to this editorial is the ASA statement on statistical significance and p-Values.

Do you see it?

A. I do.

Q. Then if you go to the second paragraph on the introduction, it says:

"Underpinning many published scientific conclusions is the concept of statistical significance, typically assessed with an index called p-Value."

Do you see that?

A. I do.

Q. (Reading.)

"While the p-Value can be a useful statistical measure, it is commonly misused and misinterpreted."

Do you see that?

A. I do.

Q. The next paragraph, it says, second sentence:

"The issues touched on here affect not only research, but research funding, journal practices, career advancement, scientific education, public policy, journalism, and law."

Do you see that?

A. I do.

Q. Let's go to the second statement that the ASA makes on statistical significance. It says:

"P-Values do not measure the probability that the studied hypothesis is true or the probability that the data were produced by random chance alone."

Do you see that?

A. I do.

Q. Do you agree with that?

A. I do.

Q. (Reading.)

"Researchers often wish to turn to a P-Value into a statement about the truth of the null hypothesis or about the probability that random chance produced the observed data. The p-Value is neither. It is a statement about the data in relation to a specified hypothetical explanation and is not a statement about the explanation itself."

Do you see that?

A. I do.

Q. Do you agree with that?

A. There is a lot there. It depends upon the context for this. When you say -- if you want to turn it into a statement about the truth of a null hypothesis, it's not literally that. It's the chance you are willing to take to get the wrong answer. So a

lot of this I think is very confusingly described by people, but these particular words I agree with them.

Q. The next point is:

"Scientific conclusions and business or policy decisions should not be based on whether p-Value crosses a specific threshold. Practices that reduce data analysis or scientific inferences to a mechanical bright line rule such as p-Value less than .05 for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision-making. A conclusion does not immediately become true on one side of the divide or false on the other."

Do you see that?

A. I do.

Q. Do you agree with it?

A. Generally speaking, you can reach the wrong conclusion. But I would say every single drug that you and I take that has been approved by the FDA requires a p-Value of less than .05. Even if you philosophically disagree with hypothesis testing or some of the principles, this is the world we live in.

Q. Doctor, drug approval is a different issue than we're facing here. We are trying to decide whether or not the epidemiologic data on balance supports a conclusion that there is an association and a

consistency --

A. It is not at all a different issue. It is a different application. It's the same topic and the same topic is if you set up a hypothesis and test it, do you accept or reject the hypothesis?

My point is the FDA may be doing something that is imperfect, but that is the world we live in. That JAMA article we looked at earlier today, JAMA Oncology, their editors and the authors may be doing something imperfect, but that's the world we live in. If you want to report your results those are the rules you use right now.

Q. We're not talking about reporting the results. We're talking about interpreting the results.

Let me ask the question. I'm trying to get from you not about publishing an article, not about getting a drug approved. I'm asking you a question.

We're looking at a series of studies and trying to decide whether or not those studies, taken in the aggregate, favor an association and a consistency of association.

A. What you are showing me --

Q. There is no question pending. Let me ask you the question.

My question now is: Isn't it important to

look at the totality of the data, including confidence intervals, including p-Values, including the risk estimates, look at it all and see what patterns arise?

A. I already said that I agreed with you when you asked me that before.

Q. So you don't simply say: You know, it crosses the line, no association?

A. In which case?

Q. In the case of multiple studies. If you have multiple studies side-by-side, one having crossing 1 and all the others not crossing 1, you wouldn't say that was not an association. Correct?

A. I think you are either misunderstanding something or you are trying to be confusing.

First of all, I don't think the authors of that paper misstated it when they said there was no association when they reported that, and it is the same hypothesis testing principle that's used when you combine studies into one.

For example, the meta-analysis we looked at, the meta-analyses combine a pooled estimate, and they provide a p-Value based on the same principle of hypothesis testing. We looked at that forest plot. It tells you something. It doesn't tell you everything. And these things we're looking at here

don't tell you what to do in this circumstance.
Q. Doctor, right after you filed your expert report, the American Statistical Association came out with a journal with 42 articles dealing with this very issue, did it not?
A. It did.
Q. And it devoted the entire journal to this issue because of what it described as a serious problem with the use or the misuse of statistical significance. Correct?
A. That was one of the motivations.
Q. And one of the articles that came out of that, an editorial that I'm going to show you. It is Exhibit 13.

Doctor, I placed in front of you, this is Diette Exhibit No. 13. This is an article that accompanied those 42 articles, but it happened to appear in the journal Nature.

Do you see it?
A. I do.
Q. It is signed by, among others, Sander Greenland. Correct?
A. That's correct.
Q. Dr. Greenland is the co-author on the book of epidemiology that we talked about before. Is that

correct?
A. That's correct.
Q. And Sander Greenland you know within a week of this being circulated, 800 statisticians and different researchers and epidemiologists signed onto this. Correct?
A. I think that's correct.
Q. And it was widely circulated including amongst the Johns Hopkins community. Correct?
A. You showed me -- your colleague showed me something from our ICTR website that showed that it had been posted there.
Q. If anyone were to describe Dr. Rothman and Dr. Greenland and any of these people as outliers, would that be accurate?
A. In what way?
Q. Pariahs in the epidemiology community?
A. That's not a term I use. There is no reason to disparage them.
Q. Okay. Now, in this article they describe what they call a pervasive problem, and they say:
"Let's be clear about what must stop: We should never conclude that there is no difference or no association just because a p-Value is larger than a threshold such as .05 or equivalently because a

confidence interval includes zero."

Do you see that?

A. I do.

Q. "Neither should we conclude that two studies conflict because one has a statistically significant result and the other does not. These errors waste research testify efforts and misinform policy decisions."

Do you see that?

A. I do.

Q. Do you agree with the authors that you should not -- epidemiologists must not say that studies conflict because one has a statistically significant result and the other one does not?

A. I don't automatically agree with that. I think you have to look at the context for this. I think you showed me this is an editorial in a different journal from Nature, which if you look at the exact same journal issue, you will see that they provide instructions to the authors on how to report their p-Values and how to report their confidence intervals. These are interesting ideas you are presenting. I'm not sure whether it is going to be the Court's job to decide whether or not this has taken hold.

But I can tell you that in the current world I

work in of epidemiology and medicine we rely on p-Values, we rely on 95 percent confidence intervals, and I can't send a paper to a publication and say: By the way Sander Greenland said I shouldn't be doing this, so I don't want you to look at this.

Q. Do you understand that we are suggesting you jettison any concept of statistical significance?

A. I can't tell what you're suggesting that you're not saying now.

Q. What he's saying here is you don't misuse it. You don't conclude the two studies conflict because one is statistically significant and one is not.

A. It also says that you shouldn't use a p-Value threshold such as .05. Unfortunately, that's the world we live in. To me this is like if you decided a jury trial of 12 people is the wrong way to do law. Maybe there is a better way. But I assume at the moment you use 12 people in the jury pool.

This is the same thing. There could be a better way, but at the moment these are not the rules of the game. These are somebody's opinion about what might happen.

Q. Doctor, if you go back to the American Statistical Society's statement, you have articles going back to the 1960s that support the misuse. You

can take a look at it. There are footnotes here going back to the 1960s and '70s talking about that epidemiologists should not do what you are doing.

A. No. What I told you earlier -- at least I've told the Court earlier -- was this is an issue we have been discussing ever since I have been in this field. This is over 20 years. It is a very interesting issue, and it may at some point change.

You are cherry-picking a few quotes that are opportunistic here. But if you read the entire introduction to that journal you are talking about, you are going to see a lot of different opinions including questions like: Are we suggesting that we abandon P-Values? And they say no, and they go on and on and say: Well, what should the substitute be? There are at least seven or eight major ideas of what the substitute should be and they have not been endorsed yet.

Q. I really need you to focus on what I'm asking. I'm asking, using statistical significance to define consistency. I'm not asking you to publish a paper. I'm not asking you to get a drug approved. I'm not asking you what it takes to get a paper published. I'm asking you how do you interpret the results when you're combining studies together.

So if you would stay focused on that, I'm going to ask you a question.

The next question goes to the next page. They have a statement here that says:

"Beware of false conclusions."

If you look at the chart, they give a generic example, and the generic example are two studies: One study they are keeping the point estimate exactly the same. Correct?

A. That's correct.

Q. One study has a tight confidence interval not crossing 1?

A. That's correct.

Q. The other one has a longer confidence interval crossing 1?

A. That's correct.

Q. And it would be wrong to say you look at this little tail right here and say that these two studies are inconsistent because this study crosses 1. Correct?

A. Well, there is obviously some difference in those studies, and one has greater variability than the other. They both have the same point estimate but you wouldn't look at those and say they are identical because they are not.

Q. Consistency doesn't imply you have to have identical studies results. How often does that happen?
A. Still, there is an inconsistency here.
Q. But to say that these two studies are inconsistent for the purpose of a Bradford Hill analysis, are you saying these two studies are inconsistent?
A. They might or might not be. I would say more than just what you have on the slide there. But what I would say is that if you looked at my slide from earlier today, I'm not saying the entire consistency criterion is fulfilled by whether things are statistically significant or not. What I really focused on primarily was that the different designs produce different answers, and it is not because of something that looks like that. It's because there is a null effect from the cohort studies and not the case-control.

The one up top would not be a good description of the average case-control effect and the bottom the average cohort effect. You have to move the red dot way, way, way to the left, almost to the line of 1 there.

Q. Doctor, when you were using the example with

J&J's counsel, you were talking about one study, and you talked about how wonderful the study was. Do you remember that?

A. I did.

Q. What we are talking about here is, not evaluating internally one study but comparing studies across a continuum of 40 years in multiple countries, multiple researchers, multiple different designs. Correct?

A. Correct.

Q. And so when you are comparing studies as opposed to looking internally within a study, you have to have some metric to kind of understand what those studies are telling you. True?

A. Some metrics help.

Q. What you are doing, what I think you are saying is if it's statistically significant -- I wrote this down -- counsel wrote it down. If it's 1, it's no association; and if it is no association, it is inconsistent with a study that shows a positive association.

Is that what you are saying or not?

A. That's literally what that study language was.

Q. And what I'm asking you, is: Are these 800 statisticians and the people at the American

Statistical Association, you have one study and you have a consensus statement, what are we to make of that, Doctor?

A. There is no consensus statement. There are 800 people who signed onto the proposition we should look into this and consider this. If you read the entire front end of that document from the statistical association, you will see lots of good ideas in there, and it is not a prescription for what to do. It's a call for considering potentially other ways of doing business.

Q. Doctor, they are not saying this is a call for what not to do. Back up to the prior page.

They are not saying what they are calling not to do. They are saying, let's be clear about what must stop.

A. You are reading from a different document.

Q. Doctor, wouldn't you agree with me, when you go back and take a look at the studies, that you have to use people like you and Dr. McTiernan, Dr. Siemiatycki, and Dr. Merlo, they have to use their own judgment when looking at this plot. There is no mechanical way of doing it.

Is that true when you look at the forest plot? If it were that easy, people like me could do it. You

have to use your professional judgment to make that call. True?

A. Make which call?

Q. About whether or not this is a consistent association.

A. Well, if you use your professional judgment correctly, you should look at those ones below that heavy horizontal line that says "cohort studies." You should remove two of the bottom three because that's redundant. It's representing a single study three times to make it look as if there are five different results. There are not.

You would take the most recent one which is the Gates one at the bottom. You would keep Gonzalez and you would keep Houghton, and I think you would reach a conclusion that those are consistently approximately null, which is exactly the same thing that the meta-analyses say when they analyze the cohort studies by themselves.

Q. And the reason why you say that is because in your mind case-control studies are inferior by design to cohort studies and some of these results cross 1. Correct?

A. No, you are incorrect. The reason I'm saying it is because that slide is misleading; and if we are

looking for consistency that I was talking about earlier, it is the consistency by study design.

So regardless of what you think you know about the ones that are all above that horizontal line, there is an inconsistency between what you see up above that line and what you see down below that line, especially when you remove the misleading two extra bars there.

Q. I want to turn my attention to the bias issue that you talked about before. It's on page 19 of 20 of your report. The study that you rely on, I tried to write it down, and you said it's a teaching study. It's the kind of study you would take and you are going to teach people about the issue of recall bias.

Do you remember that?

A. I do.

Q. It's the Schildkraut study?

A. It is.

Q. And the Schildkraut study actually was written by one of plaintiffs' experts, Dr. Moorman?

A. Correct.

Q. Your opinions on recall bias are on page 19 or 20. The study that you primarily rely on is the Schildkraut study. Correct?

A. Yes.

Q. And that's the study you told counsel is the one you would use as a teaching study?
A. Absolutely.
Q. About recall bias. Correct?
A. Without a doubt.
Q. And if you look at what Schildkraut said -- let's go to Schildkraut.
MR. TISI: It's Exhibit No. 8, your Honor.
Q. Let's just orient ourselves to what the study actually said.
This is the Schildkraut study, and it's titled the "Association Between Body Powder Use and Ovarian Cancer," and this is from the AACES. Correct?
A. Yes.
Q. Dr. Moorman is the last author which means she is the senior author on the paper?
A. Sometimes it does.
Q. The results of the study as listed above is powder use was common 62 percent of cases and 52 percent of controls. Genital powder was associated with an increased risk of epithelial ovarian cancer, odds ratio 1.44, and a dose-response relationship was found for duration of use and number of lifetime applications.
Correct?

A. That's correct.
Q. This is one of those studies that found an association and found dose-response?
A. In the combined pre-and-post 2014.
Q. And if you look at the last page -- before we talk about recall bias -- if you go to the last page, page 1416, it says:
"The results of the current study showed that genital powder use was associated with ovarian cancer risk in African-American women and are consistent with localized chronic inflammation in the ovary due to particulates that travel through a direct transvaginal route."
Do you see that?
A. I do.
Q. It's talking about biologic plausibility and association Correct?
A. Correct.
Q. "The dose-response observed for duration of genital powder use provides further evidence for the relationship between genital powder use and overall EOC risk. Our data suggest that the increased risk due to genital powder applies to both serous and nonserous histological subtypes of EOC?"
Do you see that?

A. I do.
Q. First of all, you know that Dr. Moorman was not our expert when she wrote this?
MS. BROWN: Objection, your Honor. How in the world would he know that.
Q. You read her deposition, haven't you?
A. If I did, I don't remember that fact.
THE COURT: Okay. Let's move on.
Q. Now, the issue of recall bias was addressed by her using the very data that you say is exemplary of the issue. Correct?
A. It is.
Q. And if you look at the chart, and I think the chart you referred to is chart Table II. It shows a differentiation between pre-and-post-2014 recall. Is that correct?
A. Or reporting.
Q. Or reporting.
Now, Dr. Schildkraut addressed that finding -- the Schildkraut authors addressed that finding; did they not?
A. They discussed it.
Q. And if you go to page 1416, it says, last page of the narrative, on the right-hand side:
"The authors state: Although our findings

suggest that the publicity of the class action lawsuits may have increased reporting of body powder use, our data do not support that recall bias before 2014 versus 2014 or later, which would account for the association with body powder use and EOC. It is possible that the lawsuits sharpened the memories of body power use and improved the accuracy of reported use for both cases and controls interviewed in 2014 or later."

Correct.

A. That's correct.

Q. She makes two observations: No. 1 is, this finding doesn't incriminate in any way the study that came before 2014. Correct?

A. I think this is an extrapolation from their own data. This is a current era study. They can't comment from this study based on what was true earlier.

Q. I'm asking you what they said.

A. I'm answering what I think they mean because that's the way I heard you. We just read the statement.

Q. Do you want to see what Dr. Moorman means about that?

A. Not particularly. I think this is a really

interesting study. They provide a really good rationale for looking for an interaction. They demonstrate an interaction which you just showed in Table II. They calculated the p-Value for whatever reason and showed that interaction was significant.

So it shows one of the clearest examples I have seen, and the only one in this particular matter, where there is evidence of recall bias within a particular study.

MR. TISI: Your Honor, permission to play a very brief video clip, about 30 seconds on this issue.

THE COURT: On which issue?

MR. TISI: On the issue of recall bias.

THE COURT: I'm not sure why we are doing that.

MR. TISI: I want to ask him whether or not he agrees or disagrees about what she said about her own study.

MS. BROWN: Your Honor, I would object. No. 1, I'm not sure what the relevance of that is. No. 2, there is no foundation he is even aware of that and certainly has no impact on his opinion. So I would object on lack of foundation and relevance.

MR. TISI: Your Honor, he spent a lot of time discussing her study, A. B, he spent a lot of time

criticizing her, and half of his report is spent criticizing the methodology of the plaintiffs' experts. I think hearing from what a witness for 30 seconds --

THE COURT: I'm not sure when you have a 30-second clip, I have a problem with what was said before and what was said later. That's a problem I have. So I don't think that's going to be useful. So let's move on. There is plenty of briefing on Dr. Moorman, too.

BY MR. TISI:

Q. Doctor, counsel asked you questions about IARC and whether IARC addressed the issue?

A. Which issue?

Q. The issue of bias, recall bias.

Do you remember counsel for J&J asking you whether IARC addressed the issue of whether recall bias affected the case-control studies?

A. Yes.

Q. In fact, that was not a complete reading of what IARC actually said, was it?

A. It's a very long monograph.

Q. It's not even a complete statement of what they said about recall bias; was it?

A. Let's have a look.

Q. Let's have a look.

Would you please go to Exhibit 57 in your booklet, page 409. Why don't we address all of the things IARC addressed here because it addresses bias, chance, and confounding, all three things. I intend to discuss them differently so we don't have to go back to the document.

IARC 2010 publication says the following -- explain for the record what IARC is. IARC has pulled together all the studies and looked at this issue --

THE COURT: Do you want him to explain it or do you want to explain it?

MR. TISI: I apologize.

Q. You understand that IARC looked at this issue in 2006?

A. I do.

Q. You understand they aggregated all the studies that were then available?

A. I do.

Q. You understand those results were actually published in 2010 and that's what we are looking at now. Correct?

A. That's what I understand.

Q. The first thing they looked at were some of the issues you described: Could chance explain these

observations or results?

"First, while chance cannot be ruled out as an explanation, it seemed very unlikely to be responsible for the consistent pattern of excess risks."

Do you see that?

A. Yes.

Q. First of all, they call it "consistent," correct, a consistent pattern?

A. Correct.

Q. When they talk about the risk, they talk about it in terms of consistency. Correct?

A. Correct.

Q. Next sentence:

"A second possible explanation would be recall bias, to which case-control studies may be particularly susceptible."

See that?

A. Yes.

Q. (Reading.)

"This may have been the case had there been wide spread publicity about the possible association between the use of body powder and cancer. In such circumstances, it is possible that women who had ovarian cancer could be more likely than women who did not to remember or over-report a habit, such as body

powder use, if they thought that it may have played a role in their illness."

Did I read that correctly?

A. You did.

Q. (Reading.)

"There was a flurry of publicity in the U.S.A. in the mid 1970s concerning the possible risks of cancer posed by the use of talc body powders. Following industry decision to market talc powders with no asbestos, it was the opinion of the working group that there had not been widespread public concern about this issue, at least until relatively recently. Therefore, the working group considered it unlikely that a bias could explain the set of consistent findings that stretch out over two decades."

Do you see that?

A. Yes. Would you mind just finishing.

Q. I am.

"The group believed that recall bias was possibly inherent in the case-control studies and could not rule it out."

That's the sentence your counsel provided to you. Correct?

MS. BROWN: Objection, your Honor. That's

incorrect. The IARC sentence we put out was the definition of 2-B. It was not this. So I would object to any suggestion we were somehow misrepresenting that.

THE COURT: All right.

BY MR. TISI:

Q. Let's look at what they actually said. They said:

"The working group considered it unlikely that such a bias in the context of talc and ovarian cancer was the explanation."

Did they not say that?

A. They said both that and that it was a possibility.

Q. It always is a possibility. In fact, Dr. Gordis addresses that in his book, but he says it almost never happens; doesn't he?

A. To the contrary. He actually provides excellent examples.

Q. Let's go to his book, if you have it in front of you.

THE COURT: Mr. Tisi, you have a half hour left.

MR. TISI: I'm going to move on, your Honor.

Q. Let's talk about that confounding.

IARC also addressed the issue of confounding; did it not?

A. It did.

Q. If you go to page 408 of the 2010 IARC report, it says --

MR. TISI: For the record, your Honor, that is Exhibit 8.

Q. It says:

"It is possible that confounding by unrecognized risk factors may have distorted the results. One or more factors, if they are causes of ovarian cancer and also associated with the population of perineal use of talc, could induce the appearance of an association between the use of talc and ovarian cancer where there is none."

Do you see that?

A. I do.

Q. "In order for such an unrecognized risk factor to induce the consistent pattern of excess risk in all the case-control studies, it would be necessary for the factor to be associated with perineal talc use across different countries in different decades."

That's the issue I raised before. Correct? You would have to show the confounder in the case we are talking about here with douching, it would have to

be a pattern of use that would be the same in other countries, in different decades, and under different circumstances than it was in the Nurses Health Study, in the Sister Study. Correct?

A. You would have to show it was different?

Q. You would have to show it was the same.

A. No. If you wanted douching to be the only example, you would have to show that that was also present.

Q. I'm talking about douching now.

A. I missed that. I thought we were talking about here in general about confounders.

Q. If douching was an issue, a true confounder, it would have to be an issue that was associated with talc use, not only in the sister study, but in every study in every country in every decade in which this issue was studied. True?

A. No, it wouldn't.

Q. Doctor, isn't that what IARC is saying here:

"It would be necessary for the factor to be associated with perineal talc use across different countries and different decades to be a true confounder in this circumstance"?

A. They are saying that. But what I'm saying is that douching would not have to be the confounder, and

it wouldn't have to be present in all of those other studies.

Q. You can't say to a reasonable degree of medical scientific certainty; and, in fact, you don't know that confounding explained the risks of ovarian cancer and talc in studies. True? You say it could and it may?

A. That I agree with.

Q. But you don't say that it does; do you?

A. No, most of the risks of ovarian cancer isn't known and so most of the risk has not been accounted for in any of the studies.

Q. Just to be clear, you cannot say to a reasonable degree of medical certainty that douching is a confounder for the ovarian cancer study; can you?

A. I cannot say that it is, correct.

Q. And you cannot say any of the factors that you discussed -- you cannot say that confounding is a factor that in your opinion to a reasonable degree of medical certainty affected the results of these studies; can you?

A. I think that genetic susceptibility likely did, but I can't prove it to you.

Q. Going back to the issue of recall bias, your report is very clear that recall -- that you say it

could affect. You are not telling the Court that to a reasonable view of medical certainty based upon your review of the entirety of the data that recall bias was the explanation for the increased risk in the case-control studies, are you?

A. I can't say it has to be. I can say it's demonstrated in the one study affirmatively.

Q. It's demonstrated in one study from 2014 forward, in that one study?

A. True.

Q. And most of these studies we are talking about preceded 2014. Correct?

A. And didn't examine the issue.

Q. Let me ask you this, Doctor: On the recall bias issue, you provided appendix A to your report, which was a list of articles in a public media about talc and ovarian cancer, and you used that to illustrate the possibility prior to 2014 there may have been publicity in some of these -- may have been publicity that may have affected some of these women. Correct?

A. That's correct.

Q. I can bring it up, but the record will reflect and you can take a look at it, if you wish, you made no attempt to correlate those media reports with the studies at issue in this case?

A. How would you do that?
Q. Well, you might say we have a couple of studies from Australia, and let's see whether or not there was any publicity in Australia.
A. When we're talking about Schildkraut, they didn't just say there was news reports. They literally had their own data to see whether that occurred. I can't do that even if you want me to.
Q. The next question is, let me talk about the issue of asbestos.

Would you agree with me, Doctor, there is no safe dose of asbestos in your experience?
A. I'd agree that there is no dose that's been demonstrated to be safe, but I know there has to be one.
Q. And putting the issue of causation aside, would you agree with me that if you are doing a Bradford Hill analysis and you are looking for biologic plausibility, you would agree with me on a couple of basic principles -- let me rephrase the question.

No. 1, asbestos is a known carcinogen?
A. That is correct.
Q. No. 2, there are studies linking ovarian cancer and asbestos?
A. There are with some challenges to them.

Q. No. 3, that IARC has taken the position that asbestos is an ovarian carcinogen?
A. Correct.
Q. No. 4, you are looking at talcum powder products in this case, and I think your phrase is "whatever constituents are contained in the product"?
A. Correct.
Q. Now, when you are looking at the association aspect of it, the statistical side of it, consistency strength, et cetera, it's baked into the epidemiology. Correct?
A. If we're talking about the epidemiology that relates perineal application of talcum powder and ovarian cancer. Is that correct? I'm trying to clarify because I want to make sure what question I'm answering.
Q. Yes, correct.

Let's take those statistical measures of epidemiology and put them aside for a minute and talk about biologic plausibility, which is the biology aspect of it.

Considering whether or not the association seen or suggested makes sense, you agree that's the definition of biologic plausibility. Correct?
A. It's reasonable to call it that.

Q. So if biologic plausibility, if the definition is: Does the association make sense from a biologic standpoint, if that is the definition, would the presence of a carcinogen or a probable carcinogen in the product, generally speaking, provide you with additional information, that would allow you to say this association we see, it makes sense it could be causal?

A. Not in this case, no.

Q. I'm asking generally speaking.

A. How does that work? I understand it's a hypothetical.

Q. In evaluating biologic plausibility, if I have a glass of soda and I drink it, and I get sick, and we find out in the soda there is chili powder, and somebody says, does it make sense that that soda made Chris sick, would the presence of chili powder help explain what happened to me?

A. Maybe. I don't know.

Q. You don't think it would?

A. I don't know. Does chili powder make you sick?

Q. All right. If I have a bottle of talcum powder and in this bottle are known carcinogens, and we have a pattern of epidemiology studies which demonstrate an increased risk, if I have a carcinogen in here, does

it help make sense in looking at the totality of the data that that may be an explanation?
A. Only in an abstract way. I think you would have to understand something about what kind of dose you are talking to see if it makes any sense at all.
Q. Dose goes to causation. Correct?
A. It can.
Q. I'm talking about biologic plausibility, which is a totally different concept; isn't it?
A. Not necessarily.
Q. But it can be?
A. Well, it is to me because if you said that there was a single fiber of asbestos in the bottle, and you were going to say, is that biologically plausible it causes cancer?, I would say, No. I don't know of any study that shows a single fiber can. So it's not enough to just know there's a single fiber. You would have to know something more about the dose.
Q. How many women do you know, Doctor, who use a bottle of baby powder once in their lifetime? These studies talk about lifetime use, daily use, weekly use. Correct?
A. Some do, yes.
Q. Some of these are over decades. Correct?
A. That's correct.

Q. If there is a fiber or two or five or ten in every bottle and use it for their lifetime, does that help you decide on biologic plausibility?
A. No. Dose is a very different concept than that just how many fibers are there. Dose literally means the amount of the substance that reaches the target organ.
Q. How many fibers does it take to cause mesothelioma?
A. No idea.
Q. Can one fiber cause changes that are consistent with mesothelioma?
A. Really doubtful.
Q. Can ten?
A. No idea.
Q. Would you agree with me that the presence of asbestos, for example, is relevant to the question of whether or not it is a biologically plausible mechanism for causing ovarian cancer?
A. Not without knowing something about the dose that you are talking about.
Q. Do you know that PCPC on behalf of the talc industry presented a report to the FDA in 2009 on the issue of ovarian cancer in talc?
MS. BROWN: Objection, your Honor, to the

relevance of this.

MR. LOCKE: I also object for lack of foundation.

THE COURT: What's the basis, Mr. Tisi?

MR. TISI: Let me go to a published article.

THE COURT: Okay.

BY MR. TISI:

Q. Are you familiar with an article by Huncharek and Muscat?

MR. TISI: I apologize. I grabbed the part that did not have a highlight.

A. I don't believe I have seen this one before.

MS. BROWN: Is it in the binder, counsel?

MR. TISI: It is.

Q. If you go to page 505.

THE COURT: What exhibit?

MR. TISI: Exhibit 155, your Honor.

THE COURT: What page?

MR. TISI: Page 505.

Q. This is a review, and I will represent to you that this was an article that was authored by people who were both consultants and expert witnesses for J&J.

If you look at page 505, three-quarters of the way down, there is a statement that begins with, "A

number of investigators."

Do you see that?

A. I do.

Q. Go to page 505. It says:

"A number of investigators initially implicated talc products as possible carcinogens, as before the early 1970s some talc products contained small amounts of asbestos fibers. Clearly, such products could possibly represent a carcinogenic risk secondary to asbestos contamination. It should be pointed out that this in no way implicates talc as a toxin if the problematic constituent of such products was asbestos fibers, not talc."

Do you see that?

A. I do.

Q. Putting aside the issue whether or not talc or other constituents may be carcinogenic. If it contains asbestos, that is at least a biologic explanation for the epidemiology. Is that not correct?

A. Two things: One, you still need the dose. But they are also citing an article Rohl, which has been found to be unreliable. That particular study has been found to be unreliable because they couldn't distinguish asbestiform from non-asbestiform fibers.

The premise here is based on something --

MR. TISI: I move to strike.

Q. I'm asking you the question about whether or not the presence of asbestos in talc can provide a biologic plausible explanation that would be consistent with the causal inference.

A. I think I've already answered that. This isn't any different just because we read this. My answer stands from what I said before.

Q. Your answer would be yes, that it could.

MS. BROWN: Objection, your Honor. That misstates what he testified to before.

THE COURT: I'll let him give his answer now.

BY MR. TISI:

Q. The question is: If there is presence of asbestos in the talc could that provide a biologically plausible explanation that is consistent with the causal inference?

A. I would say no unless you can tell me something about what that dose would be.

Q. I want to ask you a couple of questions about the -- do you know whether or not the other day in court, where you were told that another trial that a corporate representative of J&J --

MS. BROWN: Objection, your Honor. It sounds

like counsel is about to give information about testimony of a J&J corporate representative. I would object as inappropriate for this context, lacking foundation, and irrelevant to the inquiry before the Court and to Dr. Diette's testimony.

MR. TISI: It's not irrelevant, your Honor.

THE COURT: Let me hear what you are trying to do. I ruled before about the J&J documents testing and did not admit them. What are you trying to do now that changes that?

MR. TISI: I'm trying to demonstrate that J&J has taken the position that there is no safe dose of asbestos, none, not a fiber, not 20 fibers, not 100 fibers, and J&J's corporate representative --

THE COURT: Even if you say that this expert may not agree with it anyway. We're dealing with his opinions. He's already says he disagrees. Leave it to that and ask him his opinions.

BY MR. TISI:

Q. Doctor, do you know whether or not a reasonable scientist looking at that question could reach a contrary conclusion?

A. So I'm clear, can you say what that question is?

Q. A reasonable expert looking at talcum powder products, if it contains asbestos or a known or

potential carcinogen would be relevant to the issue of biologic plausibility?

THE COURT: I think you are asking the question regardless of dose.

Q. Regardless of dose. One fiber. Is one fiber --

A. I think a reasonable scientist would not be on firm ground if their opinion was a single fiber would cause cancer.

Q. Ten fibers?

A. I don't know what the threshold would be.

Q. Where would you be comfortable?

A. I would be comfortable if you could tell me what the dose was that the person received from the exposure that you are talking about.

Q. You don't know how many fibers it would take to make it biologically plausible?

A. No. You still would have to translate it into a dose.

MR. TISI: Your Honor, I have no further questions. Thank you very much.

MS. BROWN: With the Court's indulgence, I have ten minutes of redirect.

THE COURT: That's fine.

REDIRECT EXAMINATION

BY MS. BROWN:

Q. Just a few questions for you to finish out the day.

I want to start by picking up where counsel left off regarding a hypothetical asbestos contamination of talcum powder.

Are you with me?

A. I am.

Q. When we heard from Dr. McTiernan yesterday she testified whether talcum powder is contaminated with any alleged constituent or not, the relevant body of epidemiology to look to try to determine if there is a causal association between talc and ovarian cancer, is the talc epidemiology. Do you agree with that?

A. I do.

Q. Tell us why.

A. First of all, because it's what we have. I don't know if there is even a single study that characterized what the powder -- what it contained. In some cases the studies talked about powder that either was or wasn't talc. But even when it was talc, for the most part it wasn't identified as what the constituents were.

So I think we are left with whatever was assessed as talcum powder application is what it is. Everything about it, whether it's pure or not pure,

whatever that means, is really part of the epidemiology.

Q. Counsel asked you some questions about a slide you and I put up about IARC. Do you remember that?

A. I do.

Q. And the slide that you and I put up actually regarding IARC was not the one counsel showed you, was it?

A. That's correct.

Q. What you and I put up in fact was IARC's definition of the 2-B classification. Is that right?

A. Yes, this is part of the conclusion.

Q. And in classifying talc in the 2-B category, what are the issues that IARC raised as it relates to the evidence or the quality of the evidence of carcinogenicity?

A. They said that chance bias or confounding could not be ruled out with reasonable confidence.

Q. And what was the year of this IARC monograph?

A. It was published in 2010.

Q. Does that remain the IARC classification today?

A. Yes.

Q. And one of the articles that you discussed with the Court this morning regarding recall bias was the Schildkraut article. Is that correct?

A. It is.
Q. Do you recall the year the Schildkraut article was published?
A. It looks like 2016 is the copyright.
Q. Did IARC have the benefit of the Schildkraut results in 2010?
A. No.
Q. You were asked some questions, Dr. Diette, about a textbook by a Dr. Rothman. Do you remember that?
A. I do.
Q. And you were asked some questions about whether it would be appropriate to look at cohort studies to the exclusion of case-control studies or above and beyond case-control studies. Do you recall that?
A. I do.
Q. In performing your Bradford Hill analysis in this case, did you do that?
A. No. I looked at all the studies of both designs.
Q. Did Dr. Rothman, though, actually look at the talc epidemiology?
A. He did.
Q. And did he publish a paper about his interpretation of the talc epidemiology?
MR. TISI: Objection, your Honor, to the

phrase "publication." This is a report I was going to use if you allow me to redirect on it, I'm happy to allow her to use it, but it has not been published.

THE COURT: It's not published?

MR. TISI: It's not published. It's a report submitted to the National Toxicology Program.

THE COURT: You said in your question --

MS. BROWN: I'll rephrase.

BY MS. BROWN:

Q. Are you aware of a report by Dr. Rothman regarding the talc epidemiology in 2000?

A. Yes.

Q. Did Dr. Rothman comment on whether the relative risk seen at that time of 1.31 was strong or weak?

A. He used the characterization "weak."

Q. And is that consistent with your understanding of how a properly-applied Bradford Hill methodology would view a 1.2 or a 1.3 relative risk?

A. It is.

Q. And does Dr. Rothman also indicate some potential concerns or challenges to interpreting a relative risk of 1.3?

A. Yes. He said that bias and causation are competing explanations for the weak/positive association.

Q. And is that consistent with the, Doctor, with IARC's classification of the talc epidemiology?
A. Yes.
Q. And did Dr. Rothman also comment on whether or not the talc epidemiology indicated a dose-response?
A. If you look at the very top there, one of the things he notes is that a nearly constant feature of causal relations in epidemiology and in pathogenesis of cancer, in particular, is a monotonically increasing relation between measures of exposure and disease risk.

And then what he did is estimated what the curves looked like, two different curves, and found they were inversed, meaning the more you used, they would appear protective from ovarian cancer.

Q. Is Dr. Rothman's finding on the lack of a dose-response consistent with your review of the talc epidemiology?
A. That summarizes at the time some of the findings which at that point looked more inverse rather than flat or positive.
Q. Since the publication of Doctor --

MR. TISI: I object to the term "publication."

MS. BROWN: I'll rephrase it.

BY MS. BROWN:

Q. Since 2002 have you reviewed the talc epidemiology as it relates to whether or not a dose-response has been seen?
A. Yes.
Q. And have you found a consistent dose-response?
A. Not a consistent one.
Q. You were shown a draft screening assessment from Health Canada. Do you remember that?
A. I do.
Q. And does Health Canada in fact make a statement regarding biological gradient or dose-response?
A. Yes.
Q. And what is the conclusion as recently as December 2018 of Health Canada regarding whether or not the talc epidemiology evidence is a dose-response?
A. There are a couple just to -- the first sentence states that there is a lack of an available exposure effect relationship in the human epidemiological data.

And they also talk about Taher and colleagues isolated seven studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc. However, none demonstrated both a clear dose-response, and I think the next page says "and statistical significance."
Q. Is that consistent, Doctor, with your

application of the Bradford Hill methodology?
A. It is.
Q. You were asked some questions, Doctor, about whether this draft screening assessment was peer-reviewed. Do you remember that?
A. I do.
Q. And does the draft screening assessment in fact contain a sentence regarding what -- a statement as to that peer-reviewed process?
A. Let's see. I know we saw it earlier.
Q. The sentence beginning on the bottom of one of the risk assessment, and going to two:
"The human health portion of this assessment has undergone external peer review and/or consultation?"
Do you see that?
A. I do.
Q. Does the draft "Screening Assessment" report any additional information about what this external peer review and/or consultation may have looked like?
A. I didn't see anything else.
Q. The draft "Screening Assessment" goes on to state:
"This draft Screening Assessment focuses on information critical to determining whether substances

meet the criteria as set out in Section 64 of CEPA by examining scientific information and incorporating a weight of the evidence approach and precaution."

Do you see that, Doctor?

A. I do.

Q. And is there additional information available on Health Canada's website regarding what Health Canada views as required for this precautionary approach?

A. Yes, it's this document that you have that I have seen.

Q. And this is Health Canada decision-making framework for identifying, assessing and managing health risks.

Does it not give information about the use of a precautionary approach?

A. Yes.

Q. A key feature of managing health risks is that decisions are often made in the presence of considerable scientific uncertainty. Is that correct?

A. That's right.

Q. (Reading.)

"A precautionary approach to decision-making emphasizes the need to take timely and appropriate preventative action even in the absence of a full scientific demonstration of cause and effect."

Is that how the Health Canada organization described its precautionary approach?

MR. TISI: Your Honor, let me object. Counsel went beyond. I focused on the scientific portion of the Health Canada. She's focusing on the regulatory application of it, which are two different parts, and it's very misleading. Health Canada had two goals here, and I specifically stayed away from the one. One is whether or not it needed to take regulatory action under Canadian law to warn women and take remedial steps. That's where the precautionary issue comes into being.

The scientific analysis, which was a Bradford Hill analysis that you saw, is a separate -- was a separate analysis. I think it's misleading to conflate the two. I know this is a hearing, and we can do whatever we want in the hearing. There is no jury present, but it's misleading because that is not what the document says.

MS. BROWN: Your Honor, we are working off the document --

THE COURT: It sounds more like Mr. Tisi thinks you are going into an area that's not appropriate for redirect. That's what I was hearing.

MR. TISI: Both. A, it's inappropriate, and,

B, it's misleading.

THE COURT: I don't know if it's misleading. She is reading right from the document.

MR. TISI: I focused on the scientific aspect of it, which is the Bradford Hill aspect. She's going to the regulatory issues at Health Canada. If you look at the synopsis, the paragraph I read, which was the scientific aspect of it -- and that's why I took a little bit of time to go through and say which is the portion that was peer-reviewed, and it was the health effect section.

The other section of the document deals with the Canadian Act, whatever. And if you look at the very last paragraph that follows the scientific conclusion, they talk about, Now that we have this result, what do we do with it? I don't have the document in front of me.

THE COURT: Isn't that the point of it? The reason they went about this is to decide to take action. It's the same thing of anything we talk about, about the governmental documents, IARC. The reason these reviews are being undertaken by a governmental agency, here Health Canada, is to decide is there some action to be taken; if it's IARC, how do we classify it, what do we do.

I don't think it's inappropriate. Let's hear it and move on. I will give you a few minutes of redirect just as I gave yesterday to Mr. Williams. It's not late in the day. We'll go a little longer.

MS. BROWN: I can conclude quickly.

BY MS. BROWN:

Q. The two points here, Dr. Diette, is counsel represented that this document has been peer-reviewed; and based just on the text of what we have regarding the review process, is it clear from the document itself whether it had been externally peer-reviewed or there was some kind of consultation the details of which we don't know?

A. It's hard to tell whether it's either/or both.

Q. And in terms of the focus of the draft-screening assessment regarding the scientific information and the approach to weighing the evidence, does Health Canada speak to a precautionary approach?

A. They do.

Q. Does that precautionary approach that we just looked at, where a preventive action can be taken in the absence of full scientific demonstration of cause and effect, is that consistent -- or I think counsel used the term "very similar" or "almost the same" as a Bradford Hill causal analysis?

A. No, it clearly doesn't require a causal conclusion, that it's something that can come up short of that.

Q. Counsel asked you some questions about whether, well, Health Canada had done the same thing you had, and the two of you just reached separate conclusions.

In your review of the Health Canada document and the precautionary approach that they took, was Health Canada, the folks at Health Canada, employing the same Bradford Hill criteria as you employed?

MR. TISI: Objection. Leading I guess is okay.

MS. BROWN: I'll rephrase.

THE COURT: Leading has been the name of the game in most of the direct that I've heard this week.

Go ahead.

BY MS. BROWN:

Q. How would you compare, Dr. Diette, the Bradford Hill methodology that you employed here with the precautionary approach that Health Canada took in its assessment?

A. I'd say a couple of things. One was I didn't see they actually assessed each one of the criteria. That was one difference.

But the purpose of Bradford Hill is to

determine causation, and so it's a different exercise that precautionary principle in general requires somebody to, in essence, raise concern, but not to have definitive proof or even a substantial evidence of causation to take some action.

Q. Dr. Diette, counsel spent a fair amount of time asking you questions about consistency. Do you recall that?

A. I do.

Q. Do you recall questions suggesting you had made a determination the epidemiology was inconsistent based on a review of whether there was statistical significance in the case-control studies?

MR. TISI: Your Honor, I didn't even ask her about this slide. I think you gave counsel ten minutes.

THE COURT: She said she only needed ten. Let's be fair. The rule has been that on the redirect we talked about it, what time could be spent. I clearly indicated you could have a half hour, an hour. She just indicated she thought she only needed ten minutes. That is why we went through instead of taking a break.

MS. BROWN: This is the last topic.

THE COURT: It wasn't because she was only

allotted that.

BY MS. BROWN:

Q. Do you recall those questions about consistency and how you had made your determination of whether or not there was consistency in the talc epidemiology?

A. Yes.

Q. Dr. Diette, remind us the areas that you considered in reaching your determination about consistency.

A. Several, but looking at the total evidence that was available and what we had put up here were some examples of there being differences by study design, so that the retrospective did and the prospective did not show an association, that condoms and diaphragms contrary to what one might think did not have a consistent association with ovarian cancer, that the dose-response was really all over the map as we discussed before, tubal ligation should interrupt, wasn't consistently protective in the studies, and NSAIDS, which are antiinflammatories are not consistently associated with reduction and risk as they might be, and in fact may be associated with higher risk.

Q. Did you make your determination that there was

no consistency based solely on a review of whether or not a study reached statistical significance or did not?

A. No. I evaluated whether each one did or not. But I didn't reach my evaluation of consistency solely based on that.

Q. Did you reach your conclusions about the talc epidemiology by elevating cohort studies to the exclusion of case-control study?

A. No.

Q. Did you consider the totality of the epidemiological evidence as it relates to the hypothesis that talc can cause ovarian cancer?

A. Absolutely.

Q. Do you believe that someone properly applying the Bradford Hill criteria could possibly reach a different result than you did in this case?

A. No.

MS. BROWN: I have no further questions.

THE COURT: I'll give you a few minutes, Mr. Tisi.

RECROSS-EXAMINATION

BY MR. TISI:

Q. Counsel asked you some questions about -- and

I'm glad she did ask you some questions about -- Dr. Rothman's report in 2000. This 2000 report is 19 years ago in terms of the studies that have gone on between then and now. Correct?

A. Correct.

Q. But the general principles that he describes here are all the same. Correct? The methods?

A. I don't remember every word of that, but, certainly, at least many of the principles are the same.

Q. If you go to the second page of the document, this is Exhibit 146, under "Exposure Misclassifications," do you see that?

A. Not yet.

Q. It's on page 3.

A. Okay.

Q. J&J and PCPC and the talc industry hired Dr. Rothman to present this to the National Toxicology Program? This was J&J's expert at the time.

A. I heard that. I'm not sure whether it's right or not.

Q. They didn't contact you at any time to do this for them, right?

A. That is correct.

Q. But they did contact Dr. Rothman, and Dr.

Rothman here says:

"It is commonly believed that the validity of case-control study is worse than cohort studies, but that view is a mistaken."

Do you see that?

A. I do.

Q. (Reading.)

"The validity of the study depends on the specifics of the study design, the nature of the data, and the nature of the hypothesis the study addresses."

Do you see that?

A. I'm with you.

Q. The truth of the matter is, because of the nature of cancer, many of the studies of cancer are case-control studies. True?

A. For rare cancers especially.

Q. Ovarian cancer is a rare cancer; isn't it?

A. It is.

Q. So it's not surprising that the studies that are the ones that are most used by people who study the epidemiology of cancers are case-control studies. True?

A. It's not surprising.

Q. He gives an example, and this is helpful:

"A cohort study that examines the long-term

risk of cancer among coffee drinkers after a one-time dietary assessment of coffee consumption would suffer from weak exposure assessment. Although exposure information might be accurate at the time it was collected the exposure status of the cohort members will change over time with time and the initial measure might only poorly correlate with more meaningful measures of coffee consumption."

What he is saying here is, Doctor, if you only take the measurement once, that people's behavior changes. Right?

A. It can change.

Q. Often does change. Correct?

A. I don't know how often it does, but it can change, is the point.

Q. (Reading.)

"The effect of having a poor measure of exposure will be considerable nondifferential misclassification."

He uses the word "considerable." Correct?

A. That's correct.

Q. Now, adding to that let's say instead of studying coffee consumption, you want to study caffeine consumption, and you ask people about coffee.

Now, if you ask them about coffee, they may

answer if you are not specific enough, you would include decaffeinated coffee. Right?
A. I'm sorry?
Q. If the questionnaire says, You drink coffee, people --
A. I understand. I misheard. This has been on my mind since the Health Canada thing, which is they say that there's 8,500 consumer products that have talc in it. That's like asking about perineal talcum powder and not asking about the 8,499 other ones.
Q. But you know the cohort studies, Houghton and Gates, asked only once. Right?
A. Correct.
Q. And not only that, but they only asked about powder exposure. It could be cornstarch. It could be other kinds of powders. Right?
A. I would have to look back to see which question was used on which, but I know certain studies used that broader.
Q. And so both of those things combined have the potential of raising nondifferential or, to use Dr. Rothman's term, considerable nondifferential misclassification. Correct?
A. Correct.
Q. And that is the kind of bias -- you spent a lot

of time talking about recall bias, but that's the kind of bias that's towards the null?

A. That is correct.

Q. And that is a point that Dr. Rothman is making.

Another thing he says here, he talked about another issue you raised, which is the issue of confounding. This is 19 years ago:

"Although there are some strong risk factors for ovarian cancer, for any of them to be confounding to the extent they could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity, and some reproductive factors are poorly associated with the risk of ovarian cancer."

See that?

A. I do.

Q. (Reading.)

"But the magnitude of these associations does not appear to be high enough to induce enough confounding, even jointly, to completely explain the positive association?"

Do you see that?

A. I do.

Q. So what he is saying is, in order for the confounder to really explain the results of the study,

the confounder has to be closely correlated with, in this case talc use, closely correlated causing the disease itself, and it would have to be of an order of magnitude that would have to be high enough to explain the risk. Correct?

A. To be fair, they list four that they say the magnitude does not appear high enough to induce enough confounding. But we know most of the explanation for ovarian cancer isn't known. So the majority of the risk remains to be discovered, and all of that could be confounding.

Q. But what he is saying and whether you see IARC, whether you see Dr. Rothman, whether the study we talked about before, confounding has consistently been said unlikely done, unlikely the result to be a cause of the increased risk for the talc study. You have seen that in the literature. Correct?

A. I don't think what you said is right. We've looked at a variety of different statements on it. Some consider it possible. There is different language that different investigators have used.

Q. Counsel asked you about precautionary principles in Health Canada, and I'm going to ask -- let me ask you briefly.

Health Canada specifically excluded discussion

of asbestos in talc. Right?
A. They were focused on talc for this project.
Q. And did they say that if talc was in the asbestos, that they would categorize it in a completely different way?
A. I think you meant the other way around. I think you said if talc was in the asbestos.
Q. If asbestos was in talc, it would be a completely different issue and it would be governed by a different set of regulations?
A. I don't recall that, but I don't doubt that it would be a different mechanism.
Q. And so at least to Health Canada, the presence or absence of asbestos in talc would have made a difference. Correct? You saw that in the document.
A. In how they regulate it?
Q. Yes.
A. Yes.
Q. One other thing, in terms of what Health Canada -- in terms of precautionary principles, do you know what Health Canada is proposing to tell consumers about the risk of talc?
A. Beyond what is in these documents we looked at today?
Q. Yes. Did you look on the website?

THE COURT: He already said he doesn't know. Let's move on.

MR. TISI: So the record is clear --

THE COURT: No. We're dealing with the document. It's not part of what he's got. He only testified about the document.

Let's move on. You are not going to get it through him.

MR. TISI: I have no further questions.

Thank you for your indulgence.

THE COURT: Thank you.

You are excused, Dr. Diette.

(Witness excused.)

(Court adjourned at 3:30 p.m.)

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I N D E X

**C E R T I F I C A T E**

PURSUANT TO TITLE 28, U.S.C., SECTION 753, THE FOLLOWING TRANSCRIPT IS CERTIFIED TO BE AN ACCURATE TRANSCRIPTION OF MY STENOGRAPHIC NOTES IN THE ABOVE-ENTITLED MATTER.

S/Vincent Russoniello
Vincent Russoniello, CCR
Certificate No. 675

**M**

**P**

**U**